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(54) Title: COMBINATORIAL PROCESS FOR PREPARING SUBSTITUTED PYRROLIDINE LIBRARIES

(57) Abstract

This invention relates to a novel solid phase process for the preparation of pyrrolidine combinatorial libraries. These libraries have use for drug discovery and are used to form wellplate components of novel assay kits.

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COMBINATORIAL PROCESS FOR PREPARING SUBSTITUTED PYRROLIDINE LIBRARIES

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/024,559, filed August 26, 1996.

Field of the Invention

This invention relates to the preparation of libraries of substituted pyrrolidines by combinatorial processes. These libraries are useful for discovery of lead compounds for drug development and improved assay kits.

Background of the Invention

Traditional chemical synthesis for drug discovery is done by individually creating, isolating, and identifying candidate compounds. Companies have long relied on their historical collections of compounds and compound collections from exchange agreements as sources of diverse structures for generating lead pharmaceutical compounds.

All of these historical approaches have drawbacks. Corporate collections of compounds may have a certain bias and medicinal chemists using traditional synthetic techniques cannot synthesize hundreds or thousands of diverse compounds to find promising leads.

Combinatorial chemistry is a relatively new technique for chemical synthesis. It fills the longfelt need for a method to quickly generate highly diverse non-peptide compound libraries. Generally, diverse libraries contain compounds with a common core or scaffold which are substituted with a great variety of substituents. More recently, modern drug discovery has used the methods of combinatorial chemistry to generate large numbers (viz.,

about 10^2 to 10^6) of compounds generically referred to as "libraries."

Combinatorial chemistry may be performed in a manner where libraries of compounds are generated as mixtures with complete identification of individual compounds postponed until after positive screening results are obtained. However, a preferred form of combinatorial chemistry is "parallel array synthesis" where individual reaction products (most often individual compounds) are synthesized together, but are retained in separate vessels. For example, the library compounds are held in the individual wells of 96 well microtiter plates. Use of standardized microtiter plates or equivalent apparatus is advantageous because such apparatus is readily manipulated by programmed robotic machinery.

Generally, combinatorial chemistry is conducted on a solid phase support, normally a polymer. A selected scaffold is cleavably tethered to the solid support by a chemical linker. Reactions are carried out to modify the scaffold while tethered to the solid support. In a final step, the product is cleaved and released from the solid support.

Combinatorial chemistry evidences its utility by commercial success. Millions of dollars have been spent for recent purchases or cooperative associations of major pharmaceutical companies with small companies specializing in combinatorial chemistry (e.g., Glaxo's acquisition of Affymax, Marion Merrell Dow's purchase of Selectide, Proctor & Gamble with Houghten, Astra with Alanex, Pfizer with Oxford Asymmetry, Sandoz with Pharmacopeia, Solvay with Arqule, CIBA with Chiron, and Eli Lilly with Sphinx Pharmaceutical).

Certain chemical reactions of pyrrolidines are known.

Various aspects of pyrrolidine chemistry are known in the prior art as set out below:

A) The article, "Synthesis of Enantiomerically Pure Pyrrolidines by Stereospecific Cycloaddition of Azomethine Ylides with Enones," by Patzel, M. et al., Tetrahedron Letters., Vol. 34, No. 36, pp. 5707-5710, 1993 describes the synthesis of pyrrolidines via cycloaddition onto enones.

B) The article, "Improved Synthesis of 4-Alkoxybenzyl Alcohol Resin" by Gui-shen Lu, et. al., J. Org. Chem., 1981, vol. 46, pp. 3433-3436, describes the preparation of a Wang resin for solid-phase peptide synthesis.

C) The article, "Combinatorial Organic Synthesis of Highly Functionalized Pyrrolidines: Identification of a Patent Angiotensin Converting Enzyme Inhibitor from a Mercaptoacyl Proline Library", by Martin M. Murphy, et. al., J. Am. Chem. Soc. 1995, Vol 117, pp. 7029-7030 describes the preparation of selected functionalized pyrrolidines using 1,3-dipolar cycloaddition reactions.

D) The article, "Solid-Phase Synthesis of Proline Analogs via a Three Component 1,3-dipolar cycloaddition" by Bruce C. Hamper, et. al. Tetrahedron Letters, Vol. 37, No. 21, pages 3671-3674, 1996, describes the preparation of selected highly substituted pyrrolidines by solid phase synthesis using 1,3-dipolar cycloaddition of a resin bound azomethine ylide.

To continue exploration of new libraries for pharmaceutical and agricultural lead compounds it is necessary to develop new chemistries which permit chemical novel scaffolds to be functionalized with highly diverse groups.

Summary of the Invention

Combinatorial chemistry may be used at two distinct phases of drug development. In the discovery phase highly diverse libraries are created to find lead compounds. In a second optimization phase, strong lead compounds are much more narrowly modified to find optimal molecular configurations. The method of this invention has applicability for making both diverse libraries of pyrrolidine compounds useful for finding new lead compounds and directed libraries of pyrrolidine compounds useful for optimizing a particular desired biological activity.

This invention is an improved combinatorial process for making a library of pyrrolidine compounds.

This invention is also the combinatorial library of pyrrolidine compounds.

This invention is also a library of intermediate substituted solid supported pyrrolidine library compounds.

This invention is also the individual pyrrolidine compounds in the pyrrolidine combinatorial library of the invention.

This invention is also a novel wellplate apparatus containing the novel pyrrolidine library compounds of the invention.

This invention is also an assay kit for identification of pharmaceutical lead pyrrolidine compounds, said kit comprising (i) wellplate apparatus, and (ii) biological assay reagents, said wellplate apparatus having a combinatorial library compound in each well; wherein the improvement comprises using as a wellplate a combinatorial pyrrolidine wellplate apparatus where each well contains a pyrrolidine compound prepared by the process of the invention.

Brief Description of the Drawings

FIG. 1 is a top view of a wellplate apparatus.

FIG. 2 is a side view of a wellplate apparatus.

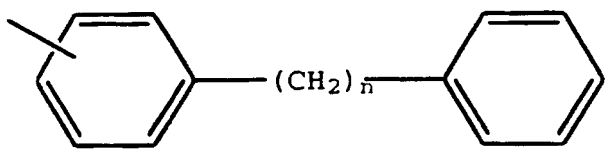
Detailed Description of the Invention

I. Definitions:

The following terms have the meaning defined below when used in this specification of the invention:

"Acidic group" means a proton donor substituent typified by $-CO_2H$, $-SO_3H$, and $-P(O)(OH)_2$.

"Aromatic group" means a substituted or unsubstituted heterocyclic group derived from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1.2-pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pryidinyl, dipyridylyl. phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl; or a carbocyclic group derived from phenyl, naphthyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (bb),



(bb)

where n is a number from 1 to 8.

"Assay kit" means an assemblage of two cooperative elements, namely, (i) a wellplate apparatus, and (ii) biological assay materials.

"Biological assay materials" are materials necessary to conduct a biological evaluation of the efficacy of any library compound in a screen relevant to a selected disease state.

"Directed Library" is a collection of compounds created by a combinatorial chemistry process for the purpose of optimization of the activity of a lead compound, wherein each library compound has a common scaffold, and the library, considered in its entirety, is a collection of closely related homologues or analogues to the lead compound (compare to "Diverse library").

"Diverse library" means a library where the substituents on the combinatorial library scaffold are highly variable in constituent atoms, molecular weight, and structure and the library, considered in its entirety, is not a collection of closely related homologues or analogues (compare to "Directed library").

"Electrophile" means an electron seeking reagent.

"Enone" means an α,β-unsaturated ketone.

"Lead compound" means a compound in a selected combinatorial library for which the Assay kit has revealed significant activity relevant to a selected disease state.

"Leaving group" means a group capable of substitution by a nucleophile.

"Library" is a collection of compounds created by a combinatorial chemical process, said compounds having a common pyrrolidine scaffold with one or more variable substituents.

"Library compound" means an individual reaction product (usually a single compound) in a library produced by the method of the invention.

"Parallel array synthesis" means a method of conducting combinatorial chemical synthesis of libraries wherein the individual combinatorial library reaction products are separately prepared and stored without prior or subsequent intentional mixing.

"Reaction zone" means the individual vessel location where the combinatorial chemical library compound preparation process of the invention is carried out and individual library compounds synthesized. Suitable reaction zones are the individual wells of a wellplate apparatus.

"Scaffold" means the invariant region (viz., pyrrolidine core) of the compounds which are members of a library.

"Simultaneous synthesis" means making of library of compounds within one production cycle of a combinatorial method (not making all library compounds at the same instant in time).

"Solid support" means a Wang resin in its hydroxyl or halogenated form. Wang resins are represented by the symbols,  and , and are prepared as described in the article by Gui-shen Lu, referenced in the "Background of the Invention" section, supra.

"Substituents" are chemical radicals (excluding hydrogen) which are bonded to the scaffold through the combinatorial synthesis process. The different functional groups account for the diversity of molecules throughout the library and are selected to impart diversity of biological activity to the scaffold in the case of diverse libraries, and optimization of a particular biological activity in the case of directed libraries.

"Reagent" means a reactant, any chemical compound used in the combinatorial synthesis to place substituents on the scaffold of a library.

"Wellplate apparatus" means a structure capable of holding a plurality of library compounds in dimensionally fixed and defined positions.

"Ylide" means a species which in its ground state has charges of opposite sign on adjacent atoms.

"Non-interfering substituent" means those groups, other than hydrogen, that do not significantly impede the solid phase process of the invention and yield stable pyrrolidine library compounds. Suitable non-interfering radicals include, but are not limited to, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, phenyl, substituted phenyl, toluyl, xylenyl, biphenyl, C_2-C_{12} alkoxyalkyl, C_1-C_6 alkylsulfinyl, C_1-C_{10} alkylsulfonyl, -$(CH_2)_m$-O-(C_1-C_{10} alkyl), aryl, substituted aryl, substituted alkoxy, fluoroalkyl, aryloxyalkyl, heterocyclic radical, substituted heterocyclic radical, and nitroalkyl; where m is from 1 to 8. Preferred non-interfering radicals are C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, phenyl, -$(CH_2)_m$-O-(C_1-C_{10} alkyl), aryl, and substituted aryl.

"Aryl" means one or more aromatic rings, each of 5 or 6 carbon atoms. Multiple aryl rings may be fused, as in naphthyl, or unfused, as in biphenyl.

"Substituted Aryl" having one or more non-interfering groups as substituents.

"Halo" means chloro, fluoro, iodo or bromo.

"Heterocycle" means one or more rings of 5, 6, or 7 atoms with or without unsaturation or aromatic character and at least one ring atom which is not carbon. Preferred heteroatoms include sulfur, oxygen, and nitrogen. Multiple rings may be fused, as in quinoline or benzofuran.

"Substituted heterocycle" means heterocycle with one or more side chains formed from non-interfering substituents.

Selected Abbreviations used in this specification:

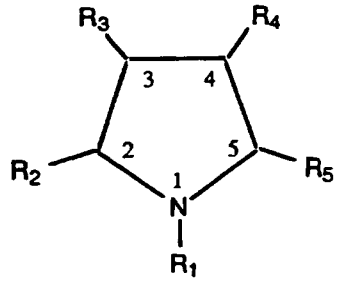
"DBU" - diazobicycloundecane

"TFA" - trifluoroacetic acid

"DMAP" - dimethyl amino pyridine

II. General description of the pyrrolidine combinatorial library:

The pyrrolidine library of the invention is a diverse combinatorial library comprising individual substituted pyrrolidine library compounds represented by the general formula (I):



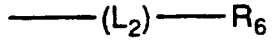
(I)

wherein;

the internal numbers in the pyrrolidine ring are used to denote substituent positions,

R_1 is an electrophilic group;

R_2 is a group represented by the formula:



where divalent linking group -(L_2)- is selected from the group consisting of,

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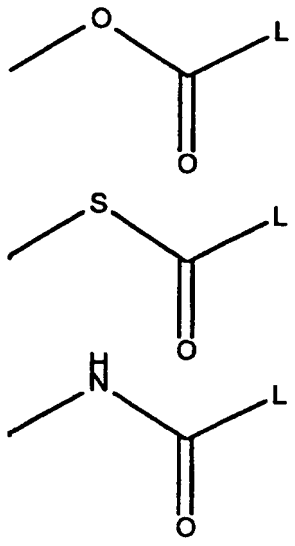
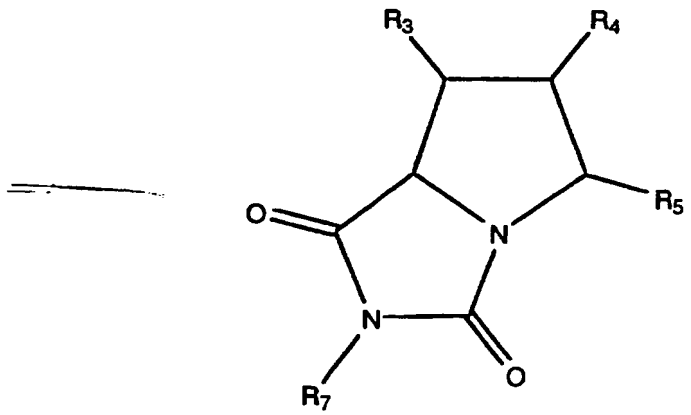


and

where "L" is the point of attachment of the pyrrolidine ring, and

where R_6 is a non-interfering substituent, and R_1 and R_2 may join together to form a hydantoin ring on the pyrrolidone nucleus as represented by formula (Ia),

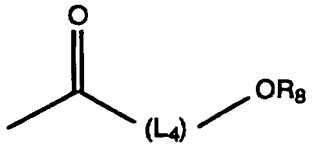


(Ia)

wherein R_7 is a non-interfering substituent;

R_3 is an aromatic group;

R_4 is a group of the general formula,



where -(L_4)- is a divalent linking group, R_8 is hydrogen or a non-interfering substituent; and

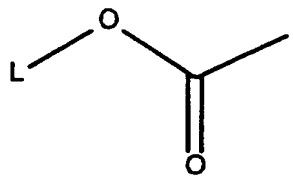
R_5 is an aromatic group.

The pyrrolidine library compounds of this invention are non-peptide, substantially non-naturally occurring molecules having a molecular weight range of from about 100 to about 700.

Preferred libraries contain pyrrolidine library compounds wherein;

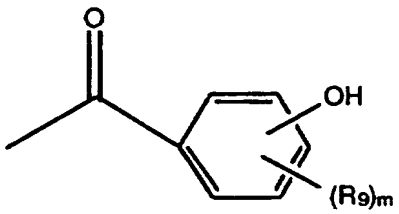
R_1 is an electrophilic group derived from an electrophilic reagent having a molecular weight of from about 30 to about 600 selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates. Particularly useful electrophilic groups are those listed in Section III, Step D, infra., of this specification. Other electrophilic groups for R_1 include, but are not limited to C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, phenyl, substituted phenyl, toluyl, xylenyl, biphenyl, C_2-C_{12} alkoxyalkyl, C_1-C_6 alkylsulfinyl, C_1-C_{10} alkylsulfonyl, -$(CH_2)_m$-O-(C_1-C_{10} alkyl), aryl, substituted aryl, substituted alkoxy, fluoroalkyl, aryloxyalkyl, carbocyclic radical, substituted carbocyclic radical, heterocyclic radical, substituted heterocyclic radical, and nitroalkyl; where m is from 1 to 8.

R_2 is a group wherein -(L_2)- is,



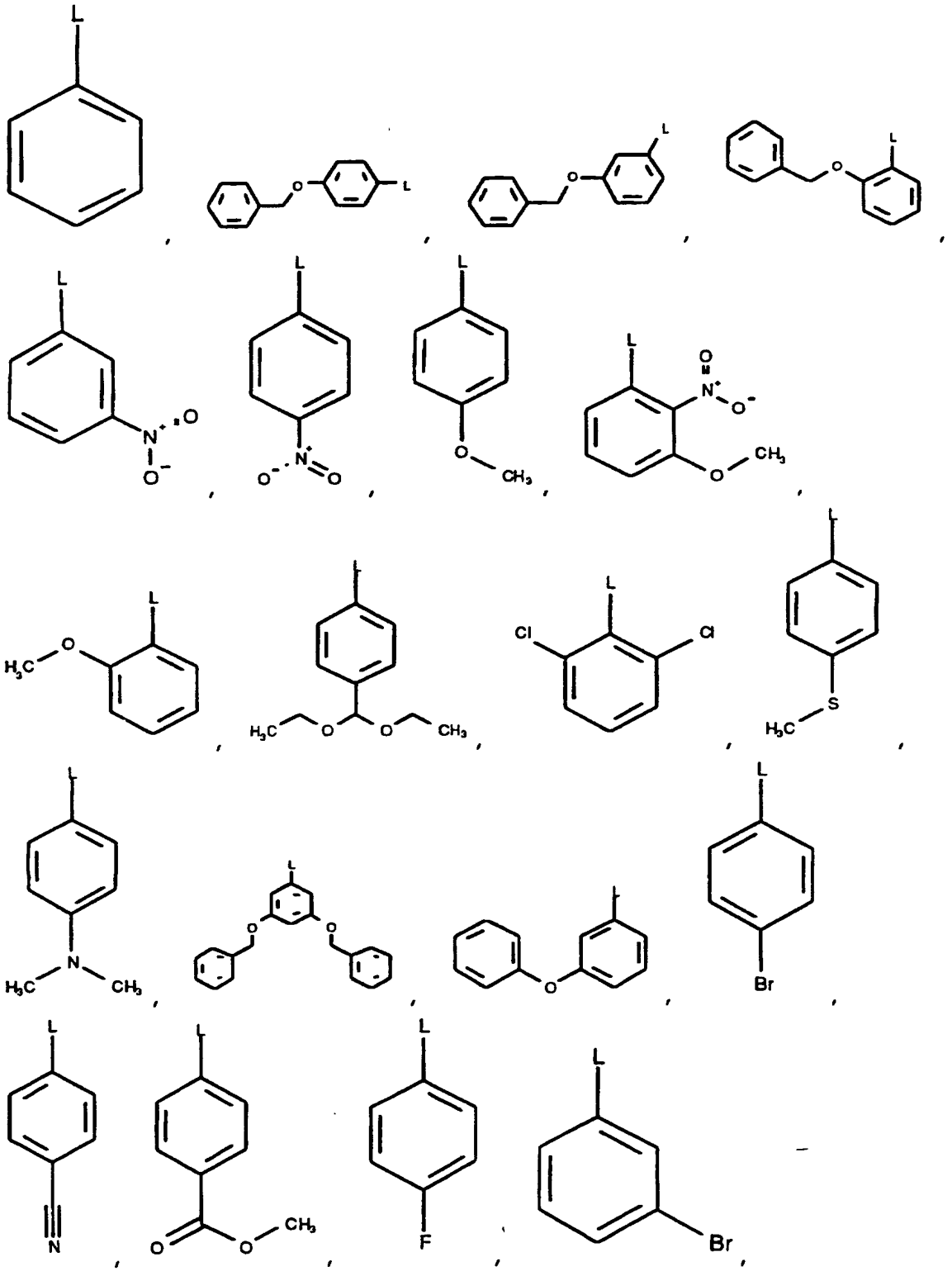
and R_6 is C_1 to C_{10} alkyl; or
R_1 and R_2 may join together to form a hydantoin
wherein R_7 is C_1 to C_{10} alkyl or an aromatic group;

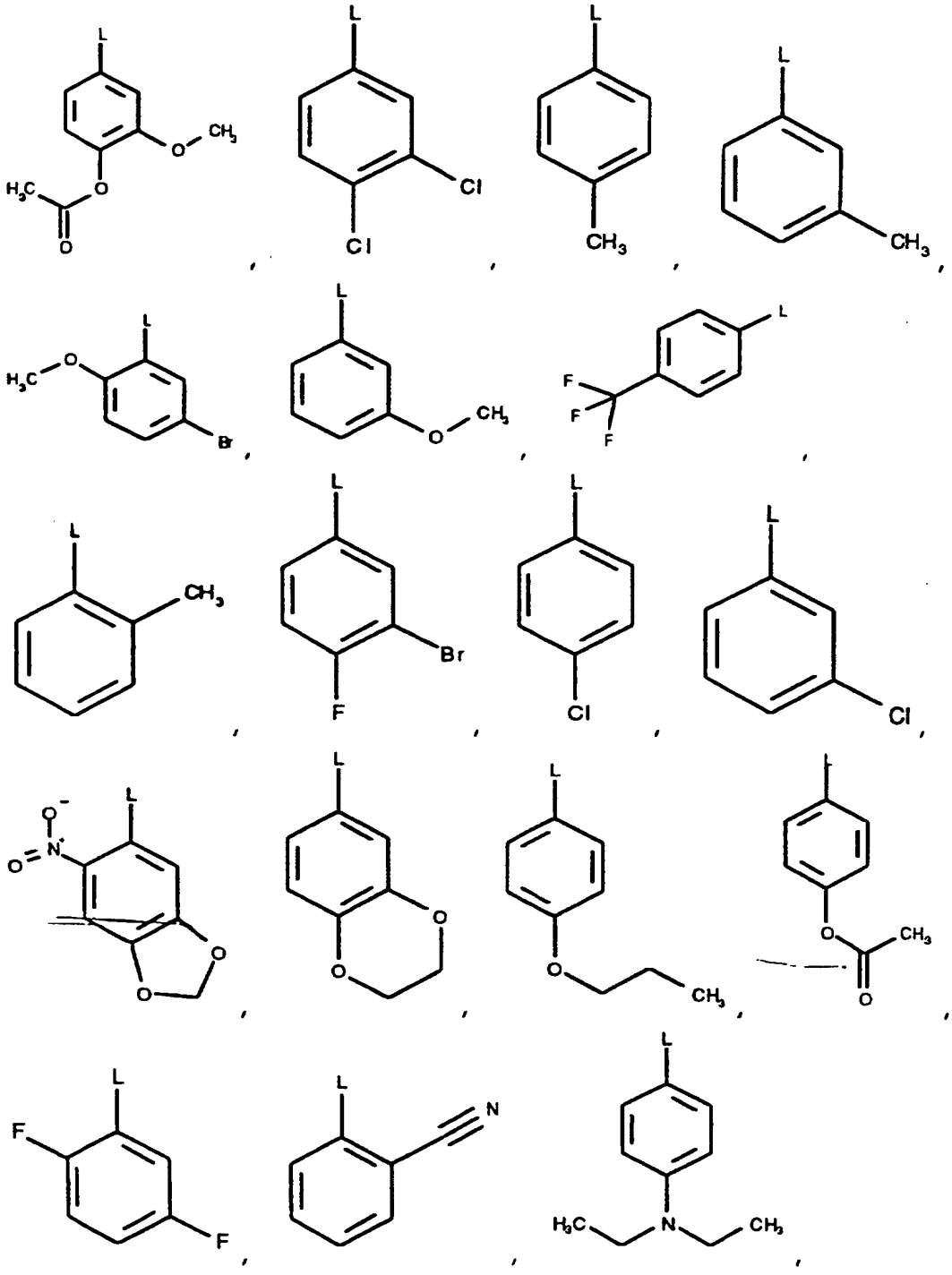
R_4 is preferably a group derived from the cleavage of the library compound from a Wang Resin, for example,

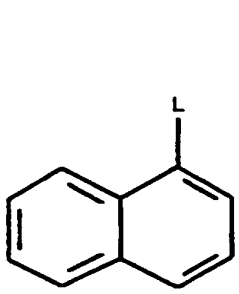
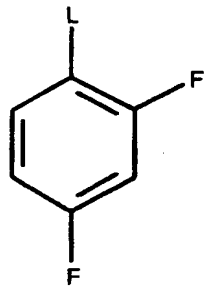
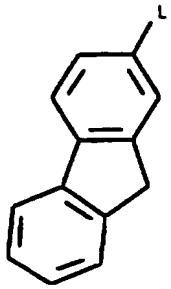
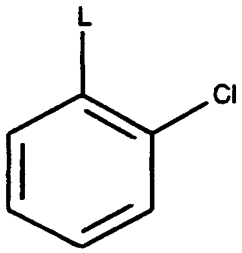


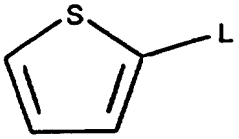
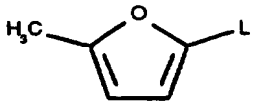
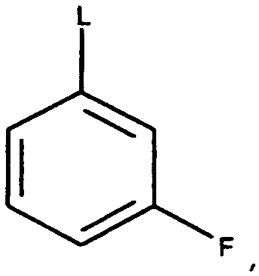
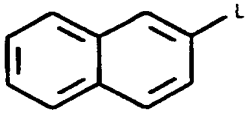
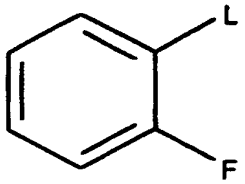
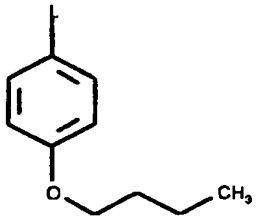
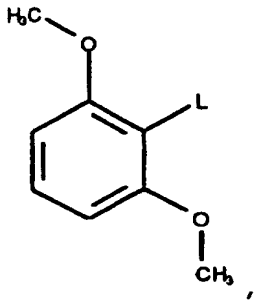
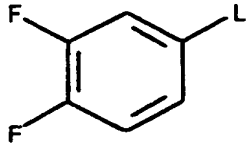
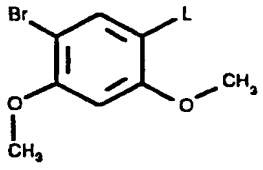
where R_9 is a non-interfering group and m is an integer from 0 to 3.

R_3 and R_5 are independently carbocyclic substituted or unsubstituted aromatic groups. Preferred groups for R_3, and R_5 are selected from the following:



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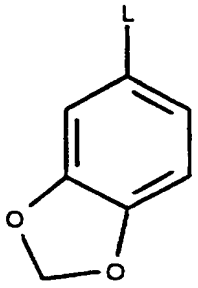
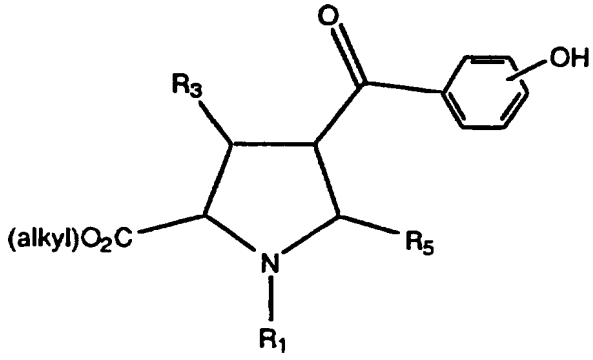

5

where "L" is the point of attachment of the above electrophilic groups.

Preferred compounds of the invention are represented by Formula (Ia) below:

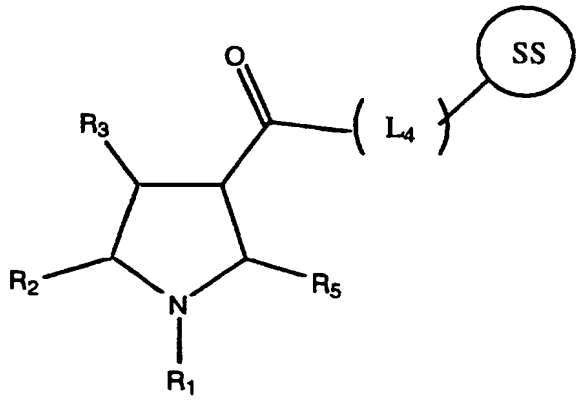


(Ia)

where R_1, R_3, and R_5 are as defined above.

III. Solid Support bound Pyrrolidine Library Compounds as Intermediates:

Products of this invention include libraries of intermediates, wherein said intermediates are the solid supported form of the substituted pyrrolidine compounds of the invention. The intermediate library contains a plurality of diverse compounds, wherein each intermediate has the formula (X):



wherein;

R_1, R_2, R_3 and R_5 and -(L_4)- as previously defined and as

is a solid support.

IV. The Process for Making the Pyrrolidine Combinatorial Library of the Invention:

Outline of Process Steps:

- Preparation of Starting Materials
- Step A - Methyl ketone functionalizing of the Wang resin solid support
- Step B - Aromatic enone formation
- Step C - 1,3-dipolar cycloaddition reaction with azomethine ylide
- Step D - Electrophilic substitution of pyrrolidine nitrogen
- Step E - Library compound cleavage from solid support.

PROCESS STEP DETAILS

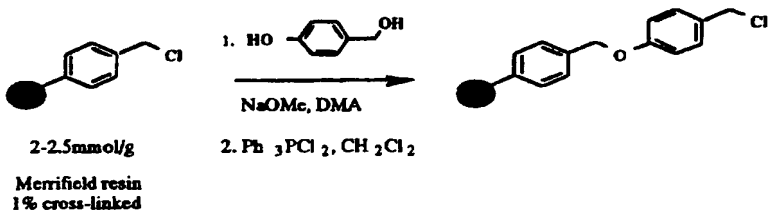
Preparation of Starting Materials:

Starting Materials:

a) Preparation of the Solid Support --

The diverse highly functionalized pyrrolidine combinatorial libraries of this invention are prepared by solid phase reactions. A preferred solid support precursor is a "Wang resin." The detailed preparation of a suitable Wang resin for conducting the process in this invention is set out in the "EXAMPLES" section, of this specification infra., the disclosure of which is incorporated herein by

reference. Preparation of a Wang resin is illustrated in the following scheme:



Wang resins permit acid catalyzed cleavage in the final step of the process.

b) Preparation of the Azomethine Ylid Reagent

Azomethine ylids are prepared from aryl amino acid imines (See, Patzel, M. reference cited in the "Background of the Invention" section of this Disclosure). The aryl imines, may in term, be prepared from a condensation reaction of aryl aldehydes and amino acid esters or amides. Aryl imines prepared glycine are preferred in the practice of this invention.

The azomethine ylid reactant is itself prepared by condensation from aryl aldehydes and amino acid esters or amides.

General Pyrrolidine Library Process Making Details:

Reaction Medium - The reaction medium may be any liquid which is non-reactive with the reactants used in the library synthesis and is a non-solvent for the solid support. It is generally advantageous to have the nucleophilic reagent and electrophilic reagent soluble in the reaction medium.

Typical reaction media useful in the processes of the invention are methanol, chloroform, dimethylacetamide,

tetrahydrofuran, dimethylformamide, methylene chloride, and acetonitrile.

The Reaction Zone - the process of the invention may be carried out in any vessel capable of holding the liquid reaction medium and having inlet and outlet means. Preferably the process of the invention is carried out in containers adaptable to parallel array syntheses. Most preferably, the pyrrolidine library is formed in standard wellplates, such as the 96 well wellplate illustrated in Fig. 1 and/or the wellplate apparatus illustrated in Fig. 2. Each well may be filled by multiple delivery apparatus, automated or robotic apparatus, any of which may be either manually or computer controlled.

The diverse pyrrolidine library of this invention may take the form of a plurality of wellplates, each wellplate having wells containing a separate reaction product (library compound). In such cases, the library compounds are conveniently identified by their wellplate number and "x" column and "y" wellplate row coordinates.

A preferred technique for practicing the process of the invention is parallel array synthesis. With parallel array synthesis individual reaction products are prepared in each of multiple reaction zones. The amount of nucleophilic and electrophilic reagents reactants introduced into each reaction zone will depend on the desired amount of each library compound that is needed for conducting biological assays, archival storage and other related needs. Typically, the desired amount of individual reaction product is from 1 microgram to 50 milligrams.

The reaction zone is maintained at a temperature and for a time sufficient to permit substantial reaction of the solid phase pyrrolidine compound and the nucleophilic and electrophilic reagents.

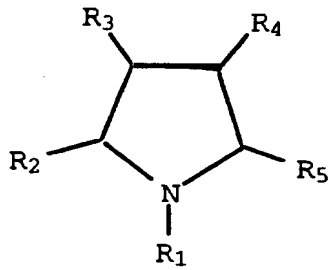
The time, temperature, and pressure of the combinatorial reaction zones used for the creation of

library compounds are not critical aspects of the invention. Reaction times for a single step of the reaction are generally from 0.1 seconds to 72 hours, with times of 1 hour to 24 hours being most often used. The temperature of the reaction may be any temperature between the freezing point and the boiling point of the liquid reaction medium, but is generally between -10°C and +60°C, with 10°C to 40°C being preferred and ambient temperatures (about 20°C-30°C) being most preferred. The reactions may be conducted at subatmospheric pressure or superatmospheric pressure (viz., 60Kg./m^2 - 21000 Kg./m^2 absolute), but ambient atmospheric pressure (about 10330 Kg./m^2, absolute) is most often used.

Endpoint determination - The completion of the reaction may be determined by a number of conventional techniques. One method is to use thin layer chromatography.

Sequence of Operation - Within each process step the addition of the reactants to the reaction zone may take place in any order. For example, the solid supported reaction product may be initially added to the reaction zone followed by addition of the electrophilic or nucleophilic reagent, or vice versa.

The principle sources for diversity in the library compounds of the invention are the groups R_1, R_2, R_3 and R_5.

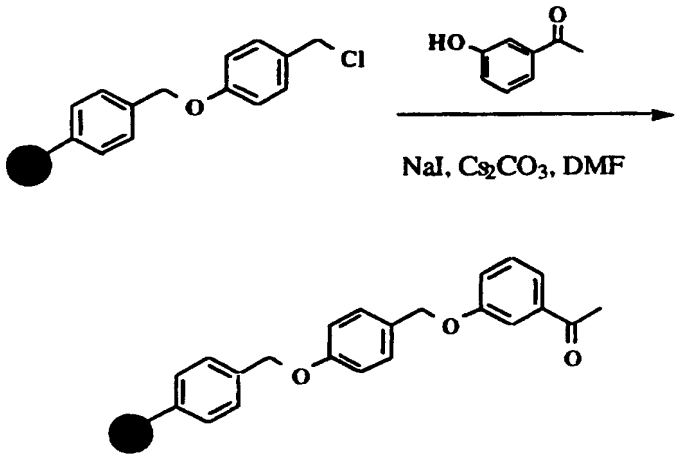


The groups R_2 and R_5 are provided in Step C of the process, the group R_1 is provided in Step D and the group R_3 is provided in Step B of the process.

--

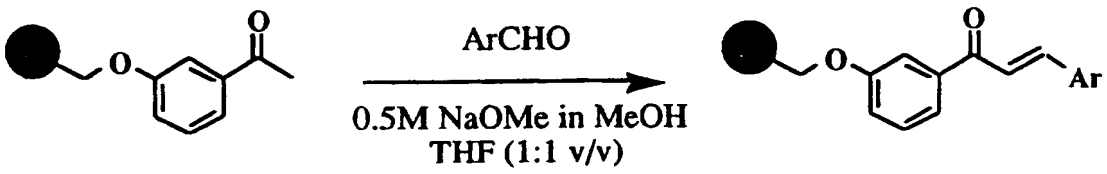
Step A.- Methyl ketone functionalizing of the Wang resin solid support

The solid support (viz., Wang resin) must first be functionalized with methyl ketone groups to permit enone formation later in the process of the invention. This is generally accomplished by reacting the solid support with a methyl ketone bearing compound. The solid support and the methyl ketone bearing compound must each have functionalities which permit reaction. For example, acetophenone may be reacted with a halogenated Wang resin as depicted by the following scheme:



Step B. - Aromatic Enone Formation:

The solid support reaction product of step A is reacted with an aromatic aldehyde as illustrated by the following scheme:



The aryl aldehyde is the source of molecular diversity for substituent R3 on the library compounds of the invention. The aromatic aldehyde may be selected from carbocyclic and heterocyclic aromatic nuclei having reactive aldehyde functionality.

Suitable aldehydes are;

2-fluorenecarboxaldehyde
n-methylpyrrole-2-carboxaldehyde
furfural
5-nitro-2-furaldehyde
5-methylfurfural
5-acetoxymethyl-2-furaldehyde
5-hydroxymethyl-2-furaldehyde
benzaldehyde
2-bromobenzaldehyde
2-fluorobenzaldehyde
pentafluorobenzaldehyde
2-chlorobenzaldehyde
2,4-dichlorobenzaldehyde
2-chloro-6-fluorobenzaldehyde
2,6-dichlorobenzaldehyde
o-anisaldehyde
2,3-dimethoxybenzaldehyde
2,3,4-trimethoxybenzaldehyde
2,4-dimethoxybenzaldehyde
2,4,5-trimethoxybenzaldehyde
2,4,6-trimethoxybenzaldehyde
2,5-dimethoxybenzaldehyde
2-ethoxybenzaldehyde
salicylaldehyde
3,5-dibromosalicylaldehyde
3-fluorosalicylaldehyde
3,5-dichlorosalicylaldehyde
3,5-diiodosalicylaldehyde
3-ethoxysalicylaldehyde

2,3-dihydroxybenzaldehyde
2,3,4-trihydroxybenzaldehyde
4-(diethylamino)salicylaldehyde
2-hydroxy-4-methoxybenzaldehyde
4,6-dimethoxy-2-hydroxybenzaldehyde
2,4,6-trihydroxybenzaldehyde
5-bromosalicylaldehyde
5-chlorosalicylaldehyde
2-hydroxy-5-methoxybenzaldehyde
2,5-dihydroxybenzaldehyde
2-carboxybenzaldehyde
2-(trifluoromethyl)benzaldehyde
o-tolualdehyde
2,3-dimethyl-p-anisaldehyde
2,4-dimethylbenzaldehyde
mesitaldehyde
2,5-dimethylbenzaldehyde
2,5-dimethyl-p-anisaldehyde
3-cyanobenzaldehyde
3-bromobenzaldehyde
3-bromo-4,5-dimethoxybenzaldehyde
5-bromo-2-methoxybenzaldehyde
3-fluorobenzaldehyde
3-fluoro-p-anisaldehyde
3-chlorobenzaldehyde
3,4-dichlorobenzaldehyde
3,5-dichlorobenzaldehyde
3-phenoxybenzaldehyde
3-(3,4-dichlorophenoxy)benzaldehyde
3-(3,5-dichlorophenoxy)benzaldehyde
3-(3-(trifluoromethyl)phenoxy)benzaldehyde
3-(4-chlorophenoxy)benzaldehyde
3-(4-methoxyphenoxy)benzaldehyde
3-(4-tert-butylphenoxy)benzaldehyde
3-(4-methylphenoxy)benzaldehyde

m-anisaldehyde
4-acetoxy-3-methoxybenzaldehyde
3,4-dimethoxybenzaldehyde
3,4,5-trimethoxybenzaldehyde
4-benzyloxy-3-methoxybenzaldehyde
3,5-dimethoxybenzaldehyde
3-benzyloxybenzaldehyde
3-hydroxybenzaldehyde
3-hydroxy-4-methoxybenzaldehyde
3,4-dihydroxybenzaldehyde
3,4,5-trihydroxy benzaldehyde
3-(trifluoromethyl)benzaldehyde
m-tolualdehyde
3-methyl-p-anisaldehyde
4-cyanobenzaldehyde
4-bromobenzaldehyde
4-fluorobenzaldehyde
4-chlorobenzaldehyde
4-acetamidobenzaldehyde
4-dimethylaminobenzaldehyde
4-diethylaminobenzaldehyde
4-phenoxybenzaldehyde
4-acetoxybenzaldehyde
p-anisaldehyde
3-benzyloxy-4-methoxybenzaldehyde
4-benzyloxybenzaldehyde
4-ethoxybenzaldehyde
4-n-butoxybenzaldehyde
1-naphthaldehyde
2-methoxy-1-naphthaldehyde
2-hydroxy-1-naphthaldehyde
4-methoxy-1-naphthaldehyde
2-naphthaldehyde
1-pyrenecarboxaldehyde
3,4-dibenzyloxybenzaldehyde

n-ethyl-3-carbazolecarboxaldehyde
2-methyl-9-acridinecarboxaldehyde
pyrrole-2-carboxaldehyde
2-thiophenecarboxaldehyde
3-methylthiophene-2-carboxaldehyde
4-bromothiophene-2-aldehyde
5-bromo-2-thiophenecarboxaldehyde
5-nitrothiophene-2-carboxaldehyde
5-methyl-2-thiophenecarboxaldehyde
3-thiophenecarboxaldehyde
indole-3-carboxaldehyde
5-methoxyindole-3-carboxaldehyde
piperonal
6-nitropiperonal
2-pyridinecarboxaldehyde
6-methyl-2-pyridinecarboxaldehyde
3-pyridinecarboxaldehyde
4-pyridinecarboxaldehyde
3-quinolinecarboxaldehyde
4-quinolinecarboxaldehyde
4-hydroxybenzaldehyde
3-ethoxy-4-hydroxybenzaldehyde
3,5-dimethyl-4-hydroxybenzaldehyde
4-biphenylcarboxaldehyde
4-(methylthio)benzaldehyde
methyl 4-formylbenzoate
4-carboxybenzaldehyde
4-trifluoromethylbenzaldehyde
4-isopropylbenzaldehyde
p-tolualdehyde
4-ethylbenzaldehyde
4-chloro-3-nitrobenzaldehyde
3,5-dinitro-2-hydroxybenzaldehyde
3-hydroxy-4-nitrobenzaldehyde
4-hydroxy-3-nitrobenzaldehyde

5-nitrovanillin
2-nitrobenzaldehyde
2,6-dinitrobenzaldehyde
6-nitroveratraldehyde
3-methoxy-2-nitrobenzaldehyde
2-chloro-6-nitrobenzaldehyde
3-nitrobenzaldehyde
5-chloro-2-nitrobenzaldehyde
2-chloro-5-nitrobenzaldehyde
5-hydroxy-2-nitrobenzaldehyde
5-nitrosalicylaldehyde
4-nitrobenzaldehyde
1,4-benzodioxan-6-carboxaldehyde
2,3-dichlorobenzaldehyde
3-ethoxy-4-methoxybenzaldehyde
3,5-bis(trifluoromethyl)benzaldehyde
2,3,6-trichlorobenzaldehyde
terephthalaldehyde monodiethylacetal
2,3-difluorobenzaldehyde
2,6-difluorobenzaldehyde
2,4-difluorobenzaldehyde
2,5-difluorobenzaldehyde
3,4-difluorobenzaldehyde
3,5-difluorobenzaldehyde
4-dimethylamino-1-naphthaldehyde
3-furaldehyde
3,4-dimethoxy-5-hydroxybenzaldehyde
2,3,5-trichlorobenzaldehyde
2,6-dimethoxybenzaldehyde
5-bromo-2,4-dimethoxybenzaldehyde
2,4-dimethoxy-3-methylbenzaldehyde
4-stilbenecarboxaldehyde
4-(3-dimethylaminopropoxy)benzaldehyde
2,4-dihydroxybenzaldehyde
3-chloro-4-fluorobenzaldehyde

2-methylindole-3-carboxaldehyde
4-hydroxy-3-methylbenzaldehyde
2-(diphenylphosphino)benzaldehyde
2,4-dinitrobenzaldehyde
4-n-propoxybenzaldehyde
1-methylindole-3-carboxaldehyde
5-bromo-2-hydroxy-3-methoxybenzaldehyde
3-bromo-4-methoxybenzaldehyde
4-acetoxy-3,5-dimethoxybenzaldehyde
3,5-dihydroxybenzaldehyde
3-methoxy-4-(4-nitrobenzyloxy)benzaldehyde
2,3-(methylenedioxy)benzaldehyde
2-hydroxy-3-methoxy-5-nitrobenzaldehyde
2-cyanobenzaldehyde
5-ethyl-2-furaldehyde
4-tert-butylbenzaldehyde
3-tetrafluoroethoxybenzaldehyde
3-carboxybenzaldehyde
1-acetyl-3-indolecarboxaldehyde
4-(trifluoromethoxy)benzaldehyde
3-bromo-4-fluorobenzaldehyde
3-(trifluoromethoxy)benzaldehyde
2-chloro-4-fluorobenzaldehyde
5-(3-nitrophenyl)furfural
2-chloro-4-hydroxybenzaldehyde
2,3,4-trifluorobenzaldehyde
2-fluoro-3-(trifluoromethyl)benzaldehyde
2-fluoro-6-(trifluoromethyl)benzaldehyde
4-fluoro-2-(trifluoromethyl)benzaldehyde
4-(dibutylamino)benzaldehyde
5-(trifluoromethoxy)salicylaldehyde
3-fluoro-2-methylbenzaldehyde
3,5-dibenzyloxybenzaldehyde
5-(4-nitrophenyl)furfural
2-chloro-3-quinolinecarboxaldehyde

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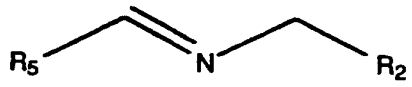
2-chloro-5-(trifluoromethyl)benzaldehyde
5-bromo-2-furaldehyde
2,3,5,6-tetrafluorobenzaldehyde
4-methyl-5-imidazolecarboxaldehyde
2-benzyloxy-4,5-dimethoxybenzaldehyde
3,5-di-tert-butyl-2-hydroxybenzaldehyde
2,4-diethoxy-m-tolualdehyde
4-tert-pentylbenzaldehyde

Alternatively, aldehyde derivative of the radicals depicted in the preceding section II, definition of R_3 and R_5 may be used as the aromatic aldehyde reactant.

Step C. - 1,3-dipolar cycloaddition reaction with azomethine ylide

The azomethine ylid reactant has the following formula;



where R_5 and R_2 are as defined above.

R_5 is an aromatic group and R_2 is an amino acid ester or amide.

The azomethine ylid reactant is the source for diversity in the R_2 and R_3 substituents of pyrrolidines represented by Formula I, supra.

The solid supported reaction product of step B is reacted with an aryl imine of an amino acid ester or an amide analog thereof. The aryl imine reactant is itself prepared by condensation of aryl aldehydes and amino acid esters or amides.

This reaction is further illustrated by the reaction scheme set out below:

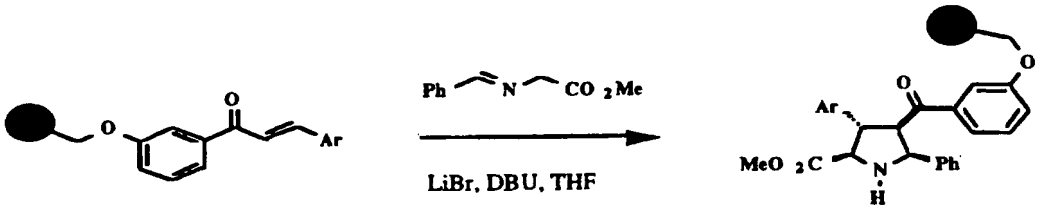
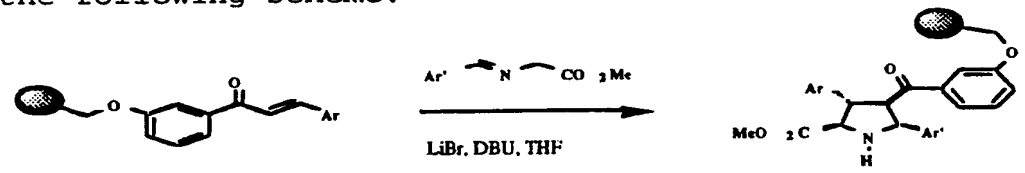
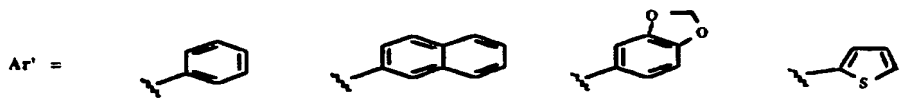


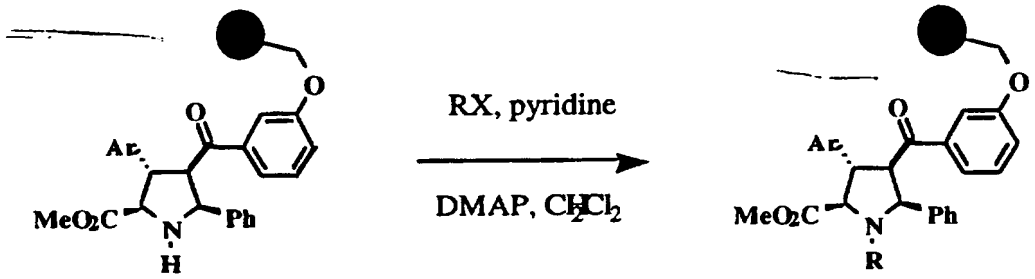
Illustration of the use of alternative imines is shown in the following scheme:





Step D - Electrophilic substitution of pyrrolidine nitrogen

The product of Step C is reacted with an electrophile. The electrophile reacts with the nitrogen atom on the pyrrolidine nitrogen ring. Alkylation and acylation reactions are suitable, for example, as show the following scheme:



Electrophilic reactants suitable for use in this step have a molecular weight of from abut 15 to 600 and are selected from organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonylhalides, organic isocyanates, and organic isothiocyanates.

Suitable electrophilic reagents for practice of this process step of the invention are set out below:

Acyl Halides --

3,5-bis(trifluoromethyl)benzoyl chloride
benzoyl chloride
2-bromobenzoyl chloride
2-fluorobenzoyl chloride
pentafluorobenzoyl chloride
2,4-difluorobenzoyl chloride
2,6-difluorobenzoyl chloride
2-chlorobenzoyl chloride
2,4-dichlorobenzoyl chloride
2,6-dichlorobenzoyl chloride
o-acetylsalicyloyl chloride
2-methoxybenzoyl chloride
2,6-dimethoxybenzoyl chloride
2-(trifluoromethyl)benzoyl chloride
o-toluoyl chloride
3-bromobenzoyl chloride
3-fluorobenzoyl chloride
3-chlorobenzoyl chloride
3,4-dichlorobenzoyl chloride
m-anisoyl chloride
3,4-dimethoxybenzoyl chloride
3,4,5-trimethoxybenzoyl chloride
3,5-dimethoxybenzoyl chloride
3-ethoxybenzoyl chloride
isophthaloyl chloride
trimesoyl chloride
3-(trifluoromethyl)benzoyl chloride
m-toluoyl chloride
3-(chloromethyl) benzoyl chloride
4-bromobenzoyl chloride
4-fluorobenzoyl chloride
4-chlorobenzoyl chloride

p-anisoyl chloride
4-ethoxybenzoyl chloride
4-n-butoxybenzoyl chloride
4-n-hexyloxybenzoyl chloride
4-heptyloxybenzoyl chloride
4-biphenylcarbonyl chloride
terephthaloyl chloride
4-(trifluoromethyl)benzoyl chloride
4-tert-butylbenzoyl chloride
p-toluoyl chloride
4-ethylbenzoyl chloride
4-n-propylbenzoyl chloride
4-butylbenzoyl chloride
4-pentylbenzoyl chloride
4-hexylbenzoyl chloride
4-n-heptylbenzoyl chloride
methyl oxalyl chloride
ethyl oxalyl chloride
heptafluorobutyryl chloride
2-acetoxyisobutyryl chloride
pivaloyl chloride
3-chloropivaloyl chloride
2-bromopropionyl chloride
2,3-dibromopropionyl chloride
2,3-dichloropropionyl chloride
o-acetylmandelic acid chloride
itaconyl chloride
methacryloyl chloride
isobutyryl chloride
2-ethylhexanoyl chloride
acetyl chloride
bromoacetyl chloride
chloroacetyl chloride
phenoxyacetyl chloride
4-chlorophenoxyacetyl chloride

methoxyacetyl chloride
phenylacetyl chloride
3,3-dimethylacryloyl chloride
cinnamoyl chloride
fumaryl chloride
ethyl malonyl chloride
tert-butylacetyl chloride
isovaleryl chloride
undecanoyl chloride
lauroyl chloride
myristoyl chloride
palmitoyl chloride
heptadecanoyl chloride
stearoyl chloride
propionyl chloride
3-bromopropionyl chloride
3-chloropropionyl chloride
hydrocinnamoyl chloride
succinyl chloride
3-carbomethoxypropionyl chloride
ethyl succinyl chloride
butyryl chloride
4-bromobutyryl chloride
4-chlorobutyryl chloride
valeryl chloride
5-chlorovaleryl chloride
adipoyl chloride
hexanoyl chloride
6-bromohexanoyl chloride
pimeloyl chloride
heptanoyl chloride
suberoyl chloride
octanoyl chloride
10-undecenoyl chloride
2-chloro-2,2-diphenylacetyl chloride

dichloroacetyl chloride
alpha-chlorophenylacetyl chloride
2-chloropropionyl chloride
2-iodobenzoyl chloride
4-iodobenzoyl chloride
cyclopropanecarbonyl chloride
trans-2-phenyl-1-cyclopropanecarbonyl chloride
cyclobutanecarbonyl chloride
cyclopentanecarbonyl chloride
3-cyclopentylpropionyl chloride
cyclohexanecarbonyl chloride
4-cyanobenzoyl chloride
2-furoyl chloride
1-naphthoyl chloride
2-naphthoyl chloride
pyrrolidine-2-carbonyl chloride
2-thiopheneacetyl chloride
trimellitic anhydride chloride
2,6-pyridinedicarboxylic acid chloride
2-quinoxaloyl chloride
2-nitrobenzoyl chloride
3-nitrobenzoyl chloride
3,5-dinitrobenzoyl chloride
4-nitrobenzoyl chloride
3,4-dimethoxyphenylacetyl chloride
3-methyladipoyl chloride
3,5-dichlorobenzoyl chloride
2,5-difluorobenzoyl chloride
3,4-difluorobenzoyl chloride
9-fluorenone-4-carbonyl chloride
3,5-difluorobenzoyl chloride
(s)-(-)-n-(trifluoroacetyl)prolyl chloride
benzyloxyacetyl chloride
acetoxy acetyl chloride
3-cyanobenzoyl chloride

2,5-dimethoxyphenylacetyl chloride
3-methoxyphenylacetyl chloride
iminodibenzyl-5-carbonyl chloride
2,4,6-trimethylbenzoyl chloride
tetrafluorosuccinyl chloride
perfluorooctanoyl chloride
diphenylacetyl chloride
alpha-methyl valeroyl chloride
methyl malonyl chloride
ethyl glutaryl chloride
5-bromovaleryl chloride
methyl adipyl chloride
3-cyclohexenecarbonyl chloride
3-isocyanato benzoyl chloride
2,4,6-triisopropylbenzoyl chloride
fluoroacetyl chloride
2-ethoxybenzoyl chloride
piperonyloyl chloride
2,4-dimethoxybenzoyl chloride
2,3,5,6-tetrachloroterephthaloyl chloride
5-(dimethylsulfamoyl)-2-methoxybenzoyl chloride
2-(4-chlorobenzoyl)benzoyl chloride
2,2-bis(chloromethyl)propionyl chloride
cinnamylidenemalonyl chloride
2-phenoxypropionyl chloride
2-phenylbutyryl chloride
2-ethylbutyryl chloride
p-tolylacetyl chloride
gamma-methylvaleroyl chloride
3,3-dichloropivaloyl chloride
1-methyl-1-cyclohexanecarboxylic acid chloride
2-(2,4,5-trichlorophenoxy)acetyl chloride
4-chloro-3-nitrobenzoyl chloride
4-methyl-3-nitrobenzoyl chloride
2,3-dichlorobenzoyl chloride

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morpholine-4-carbonyl chloride
p-chlorophenylacetyl chloride
bicyclo[2.2.1]heptane-2-carbonyl chloride
d(-)-alpha-formyloxy-alpha-phenylacetyl chloride
d(-)-alpha-phenylglycine chloride hydrochloride
trifluoroacetyl chloride
pentafluoropropionyl chloride
hexafluoroglutaryl chloride
2-chlorocinnamoyl chloride
o-methoxycinnamyl chloride
5-nitro-2-furoyl chloride
2-chlorobutyryl chloride
4-phenylazobenzoyl chloride
4-n-amyloxybenzoyl chloride
4-decylbenzoyl chloride
4-octylbenzoyl chloride
dl-2-methylbutyryl chloride
linolenoyl chloride
linolelaidoyl chloride
11h-eicosafluoroundecanoyl chloride
9h-hexadecafluorononanoyl chloride
2,3-difluorobenzoyl chloride
2-(benzoyloxymethyl)benzoyl chloride
2,2-dimethylvaleroyl chloride
3,5,5-trimethylhexanoyl chloride
phenothiazine-10-carbonyl chloride
3,4-dimethyl benzoyl chloride
(+)-p-(2-methylbutyl)benzoyl chloride
2,4-dichlorophenoxyacetic chloride
pentadecanoyl chloride
nonadecanoyl chloride
neoheptanoyl chloride
9-anthracenecarbonyl chloride
2-ethoxy-1-naphthoyl chloride
pyrrolidine carbonyl chloride

m-(chlorosulfonyl)benzoyl chloride
2-n-propyl-n-valeroyl chloride
2-chloro-4-nitrobenzoyl chloride
2-phenoxybutyryl chloride
2-chloronicotinyl chloride
6-chloronicotinyl chloride
4-(trifluoromethoxy)benzoyl chloride
2-(trifluoromethoxy)benzoyl chloride
2,6-dichloropyridine-4-carbonyl chloride
3-chlorobenzo[b]pyrrolidine-2-carbonyl chloride
4-chloromethylbenzoyl chloride
neodecanoyl chloride
(phenylthio)acetyl chloride
4-carbethoxyhexafluorobutyryl chloride
octafluoroadipoyl chloride
2-diazo-3,3,3-trifluoropropionylchloride
2-bromobutyryl chloride
arachidoyl chloride
cis-vaccenoyl chloride
11-eicosenoyl chloride
behenoyl chloride
petroselinoyl chloride
palmitoleoyl chloride
tridecanoyl chloride
2-chloro-5-nitrobenzoyl chloride
3-methylthiopropionyl chloride
methyl 4-chlorocarbonylbenzoate
anthraquinone-2-carbonyl chloride
carbazole-n-carbonyl chloride
2-nitrophenoxyacetyl chloride
2-bromo-2-methylpropionyl chloride
2-fluoro-3-(trifluoromethyl)benzoyl chloride
2-fluoro-4-(trifluoromethyl)benzoyl chloride
2-fluoro-5-(trifluoromethyl)benzoyl chloride
3-fluoro-5-(trifluoromethyl)benzoyl chloride

4-fluoro-2-(trifluoromethyl)benzoyl chloride
4-fluoro-3-(trifluoromethyl)benzoyl chloride
2-fluoro-6-(trifluoromethyl)benzoyl chloride
2,3,6-trifluorobenzoyl chloride
2,4,5-trifluorobenzoyl chloride
2,4-di(trifluoromethyl)benzoyl chloride
2,6-di(trifluoromethyl)benzoyl chloride
3-(trifluoromethoxy)benzoyl chloride
m-(fluorosulfonyl)benzoyl chloride
trans-1,2-cyclobutanedicarboxylic acid chloride
3-cyclohexylpropionyl chloride
4-ethyl-2,3-dioxo-1-piperazinecarbonylchloride
isoxazole-5-carbonyl chloride
bromodifluoroacetyl chloride
erucoyl chloride
2,4,6-trifluorobenzoyl chloride
dichlorochrysanthemic acid chloride
isononanoyl chloride
1-adamantanecarbonyl chloride
2,5-bis(trifluoromethyl)benzoyl chloride
2,3,4-trifluorobenzoyl chloride
2,3,4,5-tetrafluorobenzoyl chloride
2,4,6-trichlorobenzoyl chloride
2,4-dichloro-5-fluorobenzoyl chloride
4-methoxyphenylacetyl chloride
trans-3-(trifluoromethyl)cinnamoyl chloride
3-(dichloromethyl) benzoyl chloride
4-isocyanato benzoyl chloride
heneicosanoyl chloride
2-chloroisobutyryl chloride
trans-4-nitrocinnamoyl chloride
3,4,5-trifluorobenzoyl chloride
5-fluoro-2-(trifluoromethyl)benzoyl chloride
2,3,5-trifluorobenzoyl chloride
2-chloro-4-fluorobenzoyl chloride

(-)-alpha-chlorophenylacetyl chloride
2-(para-tolylsulfonyl)acetyl chloride
4-methyl-4-nitrohexanoyl chloride
1-chloro-4-fluorosulfonyl-2-naphthoyl chloride
2,3-dibromo-3-phenylpropionyl chloride
2-menthoxyacetyl chloride
2-phenyl-2-(phenylsulfonyl)acetyl chloride
4,4,4-trifluorocrotonyl chloride
4,4,4-trifluorobutyryl chloride
3,4-dichloro-2,5-thiophenedicarbonyl chloride
pentachlorobenzoyl chloride
4,4,7,7-tetranitrosebacoyl chloride
alpha,alpha'-dimethylsuccinyl chloride
alpha-bromoisovaleryl chloride
benzoyl chloride
oleoyl chloride
methyl suberyl chloride
gamma-linolenoyl chloride
(-)-camphanic acid chloride
4,4'-stilbenedicarbonyl chloride
chlorinated benzoyl chloride
(1r)-(+)-camphanic chloride
2-(4-nitrophenoxy)tetradecanoyl chloride
7-[(chlorocarbonyl)methoxy]-4-methylcoumarin
n,n-bis(2-chloroethyl)carbamoyl chloride
(s)-(-)-2-acetoxypropionyl chloride
linoleoyl chloride
3-chlorotetrafluoropropionyl chloride
3,4-dichloropentafluorobutyryl chloride
7h-dodecafluoroheptanoyl chloride
5h-octafluoropentanoyl chloride
perfluorononanoyl chloride
3h-tetrafluoropropionyl chloride
2-bromo-2,3,3,3-tetrafluoropropanoyl chloride
arachidonoyl chloride

pentachloropropionyl chloride
4-decenoyl chloride
tridecafluoroheptanoyl chloride
undecafluorocyclohexanecarbonyl chloride
4-n-nonylbenzoyl chloride
3-(trichlorogermyl)propionylchloride
3,4,5-triiodobenzoyl chloride
2-(phenylthio)propionyl chloride
2,2,2-triphenylacetyl chloride
d(-)-alpha-azido-phenyl acetyl chloride
4-azido-benzoyl chloride
difluoroacetyl chloride
5-chloropyrazine-2-carbonyl chloride
n-(1-naphthalenesulfonyl)-l-phenylalanyl chloride
n-(4-nitrophenylsulfonyl)-l-phenylalanyl chloride
n-(p-toluenesulfonyl)-l-phenylalanyl chloride
dimethylmalonyl chloride
methyl sebacoyl chloride
2,5-dichloropyridine-3-carbonyl chloride
3-(2,5 xylyloxy) propionyl chloride.

Additionally, acyl chorides suitable for use in the process of the invention are represented by the following formulae:

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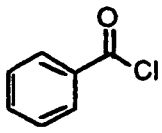
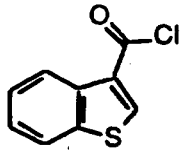
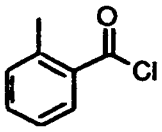
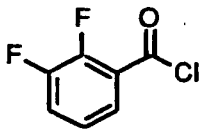
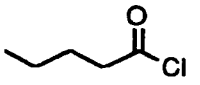
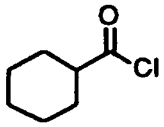
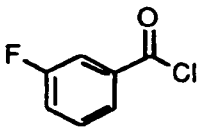
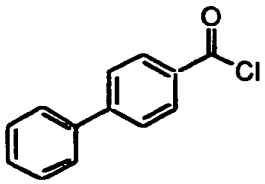
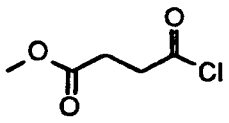
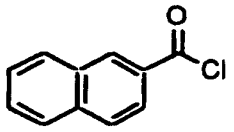
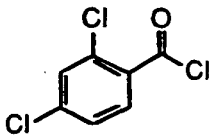
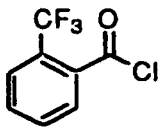













Organic Halides --

benzyl bromide
alpha-bromo-o-xylene
alpha-bromo-m-xylene
4-(tert-butyl)benzyl bromide
alpha-bromo-p-xylene
tert-butyl bromoacetate
methyl bromoacetate
benzyl bromoacetate
ethyl bromoacetate

2-bromoacetophenone
2-bromo-2'-methoxyacetophenone
2-bromo-2',4'-dimethoxyacetophenone
2-bromo-2',5'-dimethoxyacetophenone
3-methoxyphenacyl bromide
2-bromo-4'-methoxyacetophenone
2-bromo-4'-phenylacetophenone
2-bromo-4'-methylacetophenone
ethyl bromopyruvate
1-bromopinacolone
1-bromo-2-butanone
1-bromo-2,2-dimethoxypropane
1-bromo-2,2-dimethylpropane
bromoacetaldehyde dimethyl acetal
bromoacetaldehyde diethyl acetal
1-bromo-2-methylpropane
1-bromo-2-ethylbutane
2-ethylhexyl bromide
1-bromodecane
1-bromoundecane
2-bromoacetamide
iodoacetamide
4-(bromomethyl)phenylacetic acid phenacyl ester
isopropyl bromoacetate
5-bromo-2-methyl-2-pentene
3,4-difluorobenzyl bromide
2,5-difluorobenzyl bromide
3,5-bis(trifluoromethyl)benzyl bromide
2-bromo-2'-nitroacetophenone
3,5-difluorobenzyl bromide
2,4-bis(trifluoromethyl)benzyl bromide
8-bromo-1-octanol
4-(bromomethyl)phenylacetic acid
methyl (r)-(+)-3-bromo-2-methylpropionate
4-iodobutyl acetate

7-acetoxy-4-bromomethylcoumarin
4-bromomethyl-6,7-dimethoxycoumarin
2,4-difluorobenzyl bromide
methyl 2-(bromomethyl)acrylate
3-bromopropionaldehyde dimethyl acetal
(r)-(-)-3-bromo-2-methyl-1-propanol

Sulfonic Acid Esters --
ethyl trifluoromethanesulfonate
2,2,2-trifluoroethyl p-toluenesulfonate
2-chloroethyl-p-toluenesulfonate
1,3-propane sultone
5'-tosyladenosine
1,4-butane sultone
cyanomethyl benzenesulfonate
hexadecyl methanesulfonate
ethyl methanesulfonate
2-chloroethyl methanesulfonate
ethyl p-toluenesulfonate
trans-2-hydroxycyclohexyl p-toluenesulfonate
(2r)-(-)-glycidyl tosylate
(s)-(+)-2-methylbutyl methanesulfonate
(s)-(+)-2-methylbutyl p-toluenesulfonate
(s)-(+)-1-phenyl-1,2-ethanediol 2-tosylate
(2r)-(-)-glycidyl 3-nitrobenzenesulfonate
propargyl benzenesulfonate
2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate
(r)-(-)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate
(s)-(+)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate
1,2:5,6-di-o-isopropylidene-3-o-(methylsulfonyl)-alpha-d-glucofuranose
ethyl 1-2-((methylsulfonyl)oxy)propionate
(2s)-(+)-glycidyl tosylate

(2s)-(+)-glycidyl 3-nitrobenzenesulfonate
3-o-acetyl-6-o-benzoyl-5-o-(methylsulfonyl)-1,2-o-isopropylidene-alpha-d-glucofu
(r)-(-)-1-benzyloxy-3-(p-tosyloxy)-2-propanol
(s)-(+)-1-benzyloxy-3-(p-tosyloxy)-2-propanol
ethyl l-2-((trifluoromethylsulfonyl)oxy)propionate
2-(2-chloroethoxy)ethyl methanesulfonate
1-cyanoethyl p-toluenesulfonate

Organohaloformates
9-fluorenylmethyl chloroformate
phenyl chloroformate
4-chlorophenyl chloroformate
methyl chloroformate
benzyl chloroformate
vinyl chloroformate
isobutyl chloroformate
2-ethylhexyl chloroformate
ethyl chloroformate
2-bromoethyl chloroformate
2-chloroethyl chloroformate
1-chloroethyl chloroformate
allyl chloroformate
n-propyl chloroformate
butyl chloroformate
n-hexyl chloroformate
octyl chloroformate
2,2,2-trichloro-1,1-dimethylethyl chloroformate
2,2,2-trichloroethyl chloroformate
cholesteryl chloroformate
4-nitrophenyl chloroformate
4-nitrobenzyl chloroformate
(-)-menthyl chloroformate
4-t-butylcyclohexyl chloroformate
cetyl chloroformate

(+)-1-(9-fluorenyl)ethyl chloroformate
isopropyl chloroformate
3-chlorocyclohexyl chloroformate
decyl chloroformate
oleyl chloroformate
octadecyl chloroformate
butenediol bischloroformate
2-chlorobenzyl chloroformate
4-chlorobutyl chloroformate
(+)-menthyl chloroformate
4,5-dimethoxy-2-nitrobenzyl chloroformate
cyclopentyl chloroformate
t-butylcyclohexyl chloroformate
menthylchloroformate
p-tolyl chloroformate
4-bromophenyl chloroformate
4-fluorophenyl chloroformate
4-methoxyphenyl chloroformate
2-nitrophenyl chloroformate
4-methoxycarbonylphenyl chloroformate
1-chloro-2-methylpropyl chloroformate
(+/-)-1,2,2,2-tetrachloroethyl chloroformate
2,2-dichloroethyl chloroformate
myristyl chloroformate
cyclohexyl chloroformate
chloromethyl chloroformate.

Organosulfonylhalides --
1-naphthalenesulfonyl chloride
dansyl chloride
2-naphthalenesulfonyl chloride
2-acetamido-4-methyl-5-thiazolesulfonyl chloride
2-thiophenesulfonyl chloride
8-quinolinesulfonyl chloride
benzenesulfonyl chloride

pentafluorobenzenesulfonyl chloride
2,5-dichlorobenzenesulfonyl chloride
2-nitrobenzenesulfonyl chloride
2,4-dinitrobenzenesulfonyl chloride
3,5-dichloro-2-hydroxybenzenesulfonyl chloride
2,4,6-triisopropylbenzenesulfonyl chloride
2-mesitylenesulfonyl chloride
3-nitrobenzenesulfonyl chloride
p-bromobenzenesulfonyl chloride
4-fluorobenzenesulfonyl chloride
4-chlorobenzenesulfonyl chloride
4-chloro-3-nitrobenzenesulfonyl chloride
pipsyl chloride
4-nitrobenzenesulfonyl chloride
4-methoxybenzenesulfonyl chloride
4-tert-butylbenzenesulfonyl chloride
p-toluenesulfonyl chloride
trifluoromethanesulfonyl chloride
trichloromethanesulfonyl chloride
isopropylsulfonyl chloride
methanesulfonyl chloride
alpha-toluenesulfonyl chloride
trans-beta-styrenesulfonyl chloride
2,2,2-trifluoroethanesulfonyl chloride
1-hexadecanesulfonyl chloride
ethanesulfonyl chloride
2-chloroethanesulfonyl chloride
1-propanesulfonyl chloride
3-chloropropanesulfonyl chloride
1-butanesulfonyl chloride
methyl 2-(chlorosulfonyl)benzoate
2-nitro-4-(trifluoromethyl)benzenesulfonyl chloride
3-(trifluoromethyl)benzenesulfonyl chloride
1-octanesulfonyl chloride
4-(trifluoromethoxy)benzenesulphonyl chloride

(1r)-(-)-10-camphorsulfonyl chloride
d-(+)-10-camphorsulfonyl chloride
(+/-)-10-camphorsulfonyl chloride
2-nitro-alpha-toluenesulfonyl chloride.

Isocyanate Reagents --
trans-2-phenylcyclopropyl isocyanate
phenyl isocyanate
2-bromophenyl isocyanate
2-fluorophenyl isocyanate
2,4-difluorophenyl isocyanate
2,6-difluorophenyl isocyanate
2-chlorophenyl isocyanate
2,3-dichlorophenyl isocyanate
2,4-dichlorophenyl isocyanate
2,5-dichlorophenyl isocyanate
2,6-dichlorophenyl isocyanate
2-methoxyphenyl isocyanate
2,4-dimethoxyphenyl isocyanate
2,5-dimethoxyphenyl isocyanate
2-ethoxyphenyl isocyanate
2-(trifluoromethyl)phenyl isocyanate
o-tolyl isocyanate
2,6-dimethylphenyl isocyanate
2-ethylphenyl isocyanate
3-bromophenyl isocyanate
3-fluorophenyl isocyanate
3-chlorophenyl isocyanate
3,4-dichlorophenyl isocyanate
3-methoxyphenyl isocyanate
3-(trifluoromethyl)phenyl isocyanate
m-tolyl isocyanate
4-bromophenyl isocyanate
4-fluorophenyl isocyanate
4-chlorophenyl isocyanate

4-methoxyphenyl isocyanate
ethyl 4-isocyanatobenzoate
4-(trifluoromethyl)phenyl isocyanate
p-tolyl isocyanate
n-(chlorocarbonyl) isocyanate
benzoyl isocyanate
tert-butyl isocyanate
(s)-(-)-alpha-methylbenzyl isocyanate
isopropyl isocyanate
methyl isocyanate
ethyl isocyanatoacetate
octadecyl isocyanate
ethyl isocyanate
2-chloroethyl isocyanate
allyl isocyanate
n-propyl isocyanate
butyl isocyanate
cyclohexyl isocyanate
1-naphthyl isocyanate
(r)-(-)-1-(1-naphthyl)ethyl isocyanate
4-fluoro-3-nitrophenyl isocyanate
2-nitrophenyl isocyanate
3-nitrophenyl isocyanate
4-nitrophenyl isocyanate
2,6-diisopropylphenyl isocyanate
benzyl isocyanate
3-chloropropyl isocyanate
ethoxycarbonyl isocyanate
3,5-bis(trifluoromethyl)phenyl isocyanate
2,4,6-tribromophenyl isocyanate
2,5-difluorophenyl isocyanate
2,4,5-trichlorophenyl isocyanate
2,4,6-trichlorophenyl isocyanate
2-methoxycarbonylphenyl isocyanate
2-ethoxycarbonylphenyl isocyanate

2-isopropylphenyl isocyanate
2,3-dimethylphenyl isocyanate
4-methoxy-2-methylphenyl isocyanate
2,4-dimethylphenyl isocyanate
2,5-dimethylphenyl isocyanate
2-ethyl-6-methylphenyl isocyanate
3-cyanophenyl isocyanate
5-chloro-2,4-dimethoxyphenyl isocyanate
3-chloro-4-methylphenyl isocyanate
3,5-dichlorophenyl isocyanate
5-chloro-2-methoxyphenyl isocyanate
3,4,5-trimethoxyphenyl isocyanate
3,5-dimethoxyphenyl isocyanate
3-(methylthio)phenyl isocyanate
3-ethoxycarbonylphenyl isocyanate
3-acetylphenyl isocyanate
3,4-dimethylphenyl isocyanate
3,5-dimethylphenyl isocyanate
2-methoxy-5-methylphenyl isocyanate
3-ethylphenyl isocyanate
4-chloro-2-methoxyphenyl isocyanate
4-chloro-2-trifluoromethylphenyl isocyanate
4-chloro-3-trifluoromethylphenyl isocyanate
4-iodophenyl isocyanate
4-phenoxyphenyl isocyanate
4-ethoxyphenyl isocyanate
4-(methylthio)phenyl isocyanate
4-acetylphenyl isocyanate
4-isopropylphenyl isocyanate
4-ethylphenyl isocyanate
4-n-butylphenyl isocyanate
3-(dichloromethylsilyl)propyl isocyanate
octyl isocyanate
4-methyl-3-nitrophenyl isocyanate
4-chloro-2-nitrophenyl isocyanate

2-methyl-4-nitrophenyl isocyanate
4-methyl-2-nitrophenyl isocyanate
2-fluoro-5-nitrophenyl isocyanate
2-methyl-5-nitrophenyl isocyanate
3-bromopropyl isocyanate
2,4,6-trimethylphenyl isocyanate
2-isopropyl-6-methylphenyl isocyanate
2,6-diethylphenyl isocyanate
5-chloro-2-methylphenyl isocyanate
4-chloro-2-methylphenyl isocyanate
4-(trifluoromethoxy)phenyl isocyanate
4-trifluoromethylthiophenylisocyanate
2,4-dibromophenyl isocyanate
2,6-dibromo-4-ethylphenyl isocyanate
2,3,4,5-tetrachlorophenyl isocyanate
2-chloro-5-trifluoromethylphenyl isocyanate
2-chloro-6-methylphenyl isocyanate
2-n-carbobutoxyphenyl isocyanate
2,4,5-trimethylphenyl isocyanate
2-methyl-6-(t-butyl)phenyl isocyanate
2-ethyl-6-isopropylphenyl isocyanate
3-chloro-2-methoxyphenyl isocyanate
3-chloro-2-methylphenyl isocyanate
3-chloro-4-fluorophenyl isocyanate
4-cyanophenyl isocyanate
4-bromo-2-methylphenyl isocyanate
4-bromo-2,6-dimethylphenyl isocyanate
2,6-dibromo-4-fluorophenyl isocyanate
4-n-butoxyphenyl isocyanate
4-butoxycarbonylphenyl isocyanate
phenethyl isocyanate
2-methyl-3-nitrophenyl isocyanate
hexyl isocyanate
hexadecyl isocyanate
methylene bis(o-chlorophenyl isocyanate)

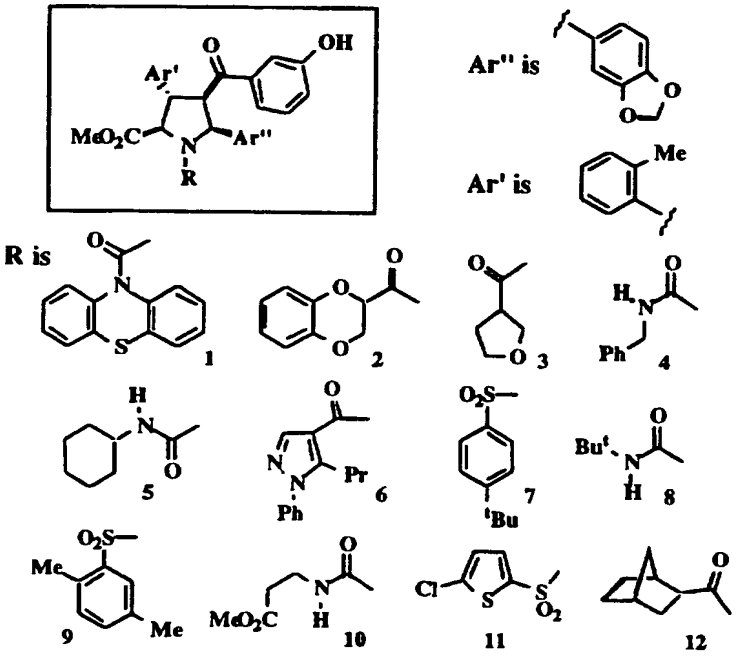
4-chloro-3-nitrophenyl isocyanate
2-chloro-4-nitrophenyl isocyanate
4,5-dimethyl-2-nitrophenyl isocyanate
2-chloro-5-nitrophenyl isocyanate
2-methoxy-4-nitrophenyl isocyanate
3-fluoro-4-methylphenyl isocyanate
5-fluoro-2-methylphenyl isocyanate
3,5-dicarbomethoxyphenyl isocyanate
2,4-dichlorobenzyl isocyanate
2-(methylthio)phenyl isocyanate
n-(methoxycarbonyl)isocyanate
n-(phenoxycarbonyl)isocyanate
2-biphenylyl isocyanate
3-iodophenyl isocyanate
4-phenylphenyl isocyanate
tetrahydro-2-pyranyl isocyanate
4-(tert-butyl)phenylisocyanate
1-(4-bromophenyl)ethyl isocyanate
isocyanatoacetic acid n-butyl ester
dodecyl isocyanate
6,7-methylenedioxy-4-isocyanate-methylcoumarin
(r)-(+)-alpha-methylbenzyl isocyanate
(+/-)-1-(1-naphthyl)ethyl isocyanate
(s)-(+)-1-(1-naphthyl)ethyl isocyanate
3,4-difluorophenyl isocyanate
2-methoxy-5-nitrophenyl isocyanate
undecyl isocyanate
ethyl 2-isocyanato-4-methyl valerate
ethyl 6-isocyanatohexanoate
ethyl 2-isocyanato-4-methylthiobutyrate
ethyl 2-isocyanatopropionate
ethyl 3-isocyanatopropionate
ethyl 2-isocyanato-3-methylbutyrate
tert-butyl 3-isothiocyanatopropionate
ethyl 2-isocyanato-3-phenylpropionate

1,3-bis(isocyanatomethyl)cyclohexane
2-(trifluoromethoxy)phenyl isocyanate
4-(chloromethyl) phenyl isocyanate
1-adamantyl isocyanate
1,3-bis(2-isocyanato-2-propyl)benzene
n-amyl isocyanate
n-heptyl isocyanate
2-chloroethyl isocyanate, [ethyl-1,2-14c]
1,1,3,3-tetramethylbutyl isocyanate
3,5-dinitrophenyl isocyanate

Organic Isothiocyanates --
cyclohexyl isothiocyanate
1-naphthyl isothiocyanate
trimethylsilyl isothiocyanate
phenyl isothiocyanate
2-bromophenyl isothiocyanate
2-fluorophenyl isothiocyanate
2-chlorophenyl isothiocyanate
o-tolyl isothiocyanate
3-bromophenyl isothiocyanate
3-fluorophenyl isothiocyanate
3-chlorophenyl isothiocyanate
m-tolyl isothiocyanate
4-bromophenyl isothiocyanate
4-fluorophenyl isothiocyanate
4-chlorophenyl isothiocyanate
p-tolyl isothiocyanate
ethoxycarbonyl isothiocyanate
benzoyl isothiocyanate
tert-butyl isothiocyanate
tert-octyl isothiocyanate
methyl isothiocyanate
benyl isothiocyanate
ethyl isothiocyanate

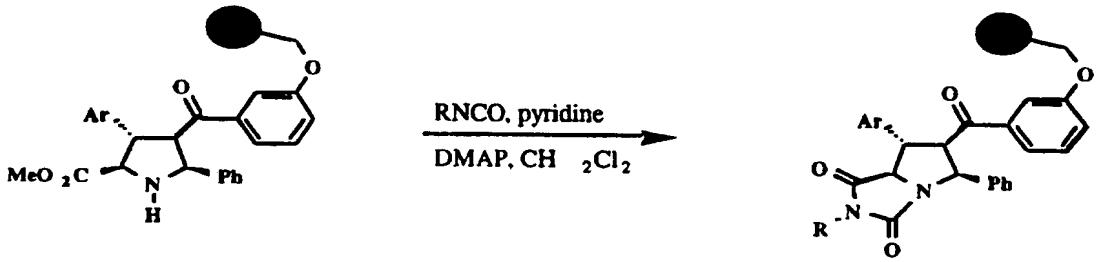
phenethyl isothiocyanate
allyl isothiocyanate

Preferred groups for acylation of the pyrrolidine nitrogen are as follows:



Part b - Formation of hydantoins

The groups R_1 and R_2 may form a hydantoin ring. When hydantoin structures are desired the alkylating/acylating agent is an isocyanate or isothiocyanate. A hydantoin forming reaction is illustrated by the following scheme:

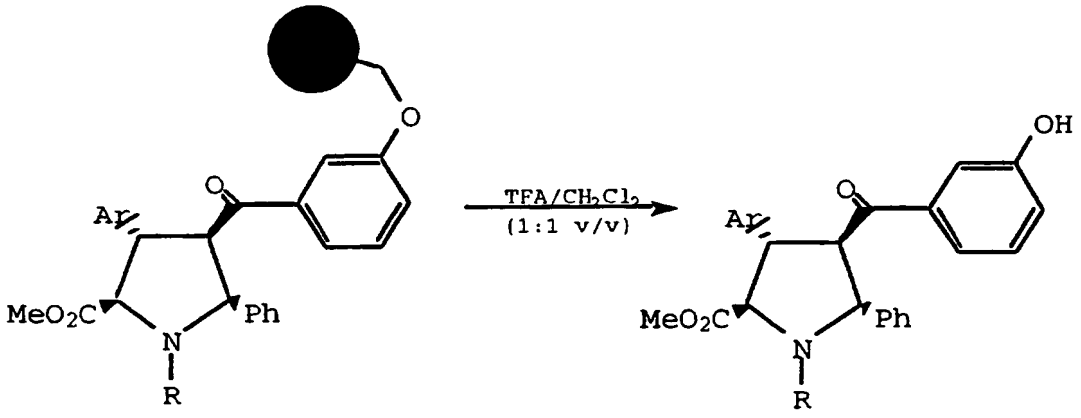


Suitable isocyanate reactants for hydantoin formation were described in the preceding listings the disclosure of which is incorporated herein by reference.

The solid support-pyrrolidine compounds produced at this step in the process of the invention are themselves valuable stable, and storable intermediates which may used when needed as sources of individual library compounds. Individual library compounds are made from these intermediates by cleavage as described in the following process Step (E).

Step E. - Library compound cleavage from Solid Support.

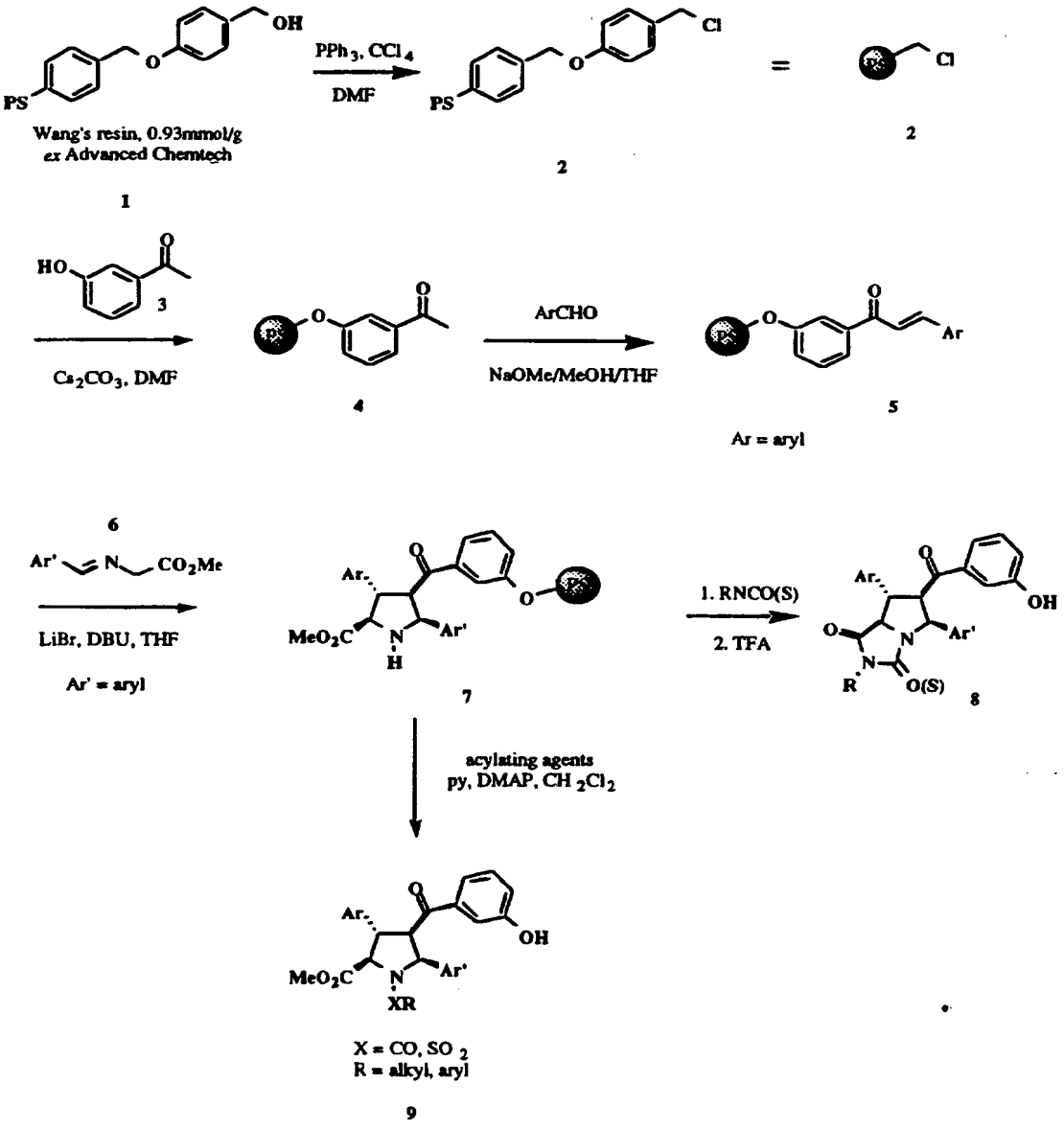
The final step of the process for preparing combinatorial pyrrolidine libraries is separation of the library compounds from its solid support. For polymeric solid supports of the Wang Resin type the decoupling is conventionally done with strong acids. For Example, the following reaction employing TFA with a Wang resin supported pyrrolidine may be used.



The final step in the pyrrolidine library forming process of the invention may be supplemented by purification techniques such as chromatography, crystallization, distillation, solvent extraction, or combinations of such techniques.

REACTION SCHEME 1

An illustrative reaction scheme illustrating all steps of the pyrrolidine combinatorial library process in combination is shown below:



EXAMPLE

The following example illustrates the preparation of a pyrrolidine combinatorial library with reference to Scheme 1, supra.

Chlorination of Wang Resin 1

Wang resin **1** (5g, 100-200 mesh, 0.93mequiv/g, *ex* Advanced Chemtech) was suspended in anhydrous DMF (60ml). To this was added triphenyl phosphine (4.88g, 18.6mmol) and then carbon tetrachloride (1.80ml, 18.6mmol). The reaction vessel was capped and placed on an orbital shaker for 2 days. At this time the reaction mixture was filtered and washed with the following: THF (200ml), THF-H_2O (1:1, 200ml), THF (200ml) and finally MeOH (200ml). The resulting white resin was dried in vacuo to provide 5.04g of chlorinated Wang resin **2**. Anal. found: C, 87.46, H, 7.45, Cl, 2.83.

Coupling of 3-Hydroxyacetophenone 3 to Chlorinated Wang Resin 2

Chlorinated Wang resin **2** (3.82g) , 3-hydroxyacetophenone (*ex* Aldrich) **3** (1.56g, 11.46mmol), cesium carbonate (3.73g, 11.46mmol) and sodium iodide (0.69g, 4.58mmol) were combined together in anhydrous DMF (50ml), capped and placed on an orbital shaker for 3 day. The reaction mixture was filtered and washed successively with the following solvents (50ml each): DMF, MeOH, H_2O, DMF-MeOH, DMF, CH_2Cl_2, MeOH. Following the final wash, the resin was dried overnight in vacuo to provide an off-white resin **4** (4.20g): IR(KBr) 1675cm^{-1}. Anal. found C, 88,34. H, 7.32.
The loading of this resin was determined by cleavage of a known amount and HPLC analysis. Thus the resin (51.2mg) was suspended in TFA (1ml) and stirred for 20hr. HPLC analysis

indicated 3.42 mg of 3-hydroxyacetophenone **3** had been cleaved. This corresponds to a loading of 0.49mmol/g.

Preparation of Enone 5 (Ar=p-$CH_{64}OMe$) by Condensation Reaction of 3-Hydroxyacetophenone Resin 4

A solution of NaOMe in MeOH (31.3ml of a 0.5M solution in MeOH, 15.6mmol) was added to a mixture of acetophenone resin **4** (2.66g) and *p*-anisaldehyde (2.36g, 15.6mmol) in anhydrous THF (30ml). The flask was capped and placed on an orbital shaker for 4 day. The reaction mixture was filtered and washed successively with the following solvents (50ml of each): THF, MeOH, THF, MeOH and finally THF. The resin was dried with air pulling through the Buchner funnel to give 3.0g of a light yellow resin **5** (Ar=p-C_6H_4OMe).
A small sample was suspended in TFA and stirred for 20 hr. The supernatant liquid was decanted and evaporated. The resulting oil was re-evaporated from methylene chloride several times to give an off white solid. ^1H NMR ($CDCl_3$) of this material was identical to a sample of enone prepared independently by standard solution synthesis.

Preparation of Pyrrolidine 7 (Ar=p-C_6H_4OMe) *via* 1,3-Dipolar Cycloaddition of Imine 6 (Ar'=Ph)

Resin **5** (Ar=OMe) (1g) was suspended in anhydrous THF. To this was added sequentially imine **6** (Ar'=Ph) (434mg as a solution in dry THF), LiBr (255mg, 2.94mmol) and DBU (372mg, 2.45mmol). The reaction mixture was slowly stirred for 3 day at which time the resin was filtered and washed successively with MeOH, THF, MeOH, THF, MeOH, THF, CH_2Cl_2 and air dried to give resin **7**.

Acetylation of Pyrrolidine Resin 7 (Ar=p-C_6H_4OMe, Ar'=Ph)

Resin **7** (Ar=pC_6H_4OMe, Ar'=Ph) (300mg) was suspended in anhydrous methylene chloride. To this was added DMAP (3mg), pyridine (190µl, 2.35mmol) and acetyl chloride (1.18ml of a 1M solution in methylene chloride, 1.175mmol). The mixture was stirred at ambient temperature for 20hr, at which time the resin was filtered and washed sequentially with the following solvents (10ml each): CH_2Cl_2, DMF, MeOH, DMF, MeOH, DMF, CH_2Cl_2, and further CH_2Cl_2. The resin was air dried and suspended in a 1:1 (v/v) mixture of CH_2Cl_2:TFA and stirred at ambient temperature for 20hr. The supernatant liquid was removed by filtration and the resin washed several times with methylene chloride. The filtrates were evaporated in vacuo to yield a crude brown foam (90mg). Purified by chromatography (SiO_2, 3:2 EtOAc-hexanes) to afford pyrrolidine **9** (31mg) (Ar=pC_6H_4OMe, Ar'=Ph, X=CO, R=Me). Crystallised from methanol. Anal. calcd. for C, .H, N, . Found C, .H, .N, .

Synthesis of Bicyclic Hydantoin 8 (Ar=p-C_6H_4OMe, Ar'=Ph, R=*n*-Bu)

Pyrrolidine resin **7** (Ar=p-C_6H_4OMe, Ar'=Ph) was suspended in methylene chloride containing DMAP (1mg) and pyridine (103µl, 1.28mmol). Butyl isocyanate (0.40ml of a 1M solution in methylene chloride, 0.40mmol) was added and the mixture stirred at ambient temperature for 20hr. The resin was filtered and washed sequentially with the following solvents (15ml each of): CH_2Cl_2, DMF, MeOH, DMF, MeOH, DMF, CH_2Cl_2. The resin was air dried and suspended in a 1:1 (v/v) mixture of CH_2Cl_2:TFA and stirred at ambient temperature for 20hr. The supernatant liquid was removed by filtration and the resin washed several times with methylene chloride. The filtrates were evaporated in vacuo to yield a crude brown

foam (19mg). Purified by preparative TLC (SiO_2, 3% MeOH-CH_2Cl_2) to afford bicyclic hydantoin **8** (Ar=p-C_6H_4OMe, Ar'=Ph, R=Bu) as a white solid. Crystallised from MeOH. FAB MS 499 (M+1). Anal. calcd. for $C_{30}H_{30}N_2O_5$ C, 72.27. H, 6.06. N, 5.61. Found: C, 72.38. H, 6.12. N, 5.65.

Experimental Conditions for Combinatorial Plate Synthesis

Resin Preparation

Sodium methoxide (29.13g, 0.539mol) was added to a stirred mixture of Merrifield resin **1** (80g of 2-2.5mmol/g, *ex* Acros) and 4-hydroxybenzylalcohol (66.95g, 0.539mol, ex Aldrich) in DMA. The reaction mixture was heated to 55°C for 8hr and allowed to cool. Filtered and washed (400ml, 2 times) successively with dioxane, DI water, dioxane, dioxane-DI water (1:1 v/v), dioxane, MeOH and dried to give an off-white resin (81g).

This resulting resin (81g) and dichlorotriphenylphosphorane (235g, 0.728mol) were combined in dry methylene chloride (1 litre) and stirred for 2 days, at which time it was filtered and washed successively (500ml of each) with methylene chloride, methanol, methlene chloride, methanol, methylene chloride. The resin was dried in vacuo (35°C) to afford a white resin **2** (80.1g).

Chlorinated Wang resin **2** (70.0g), 3-hydroxyacetophenone **3** (64.2g, 0.472mol, *ex* Aldrich), cesium carbonate (102.5g, 0.315mol, *ex* Fluka) and sodium iodide (23.6g, 0.157mol, *ex* Fluka) were combined in dry DMF (800ml) and stirred at ambient temperature for 3 days. The mixture was filtered and washed successively with DMF, MeOH, DI water, THF, DI water, THF, MeOH, and dried in vacuo overnight to afford a light brown resin **4** (81.2g).

Plate Synthesis

3-Hydroxy acetophenone resin **4** (35.3g) was suspended in a *ca.* 1:1 (v/v) mixture of DMF:CH_2Cl_2 (650ml) to obtain an isopicnic slurry. This was distributed to 13 x 96-well plates (0.50ml to each well, corresponds to *ca.* 27mg/well [*ca.* 29umol/well]). The wells were allowed to drain and were washed with THF *via* an 8-way manifold several times, drained and pulled dry over a vacuum plenum.

1) Condensation Reaction: To each row in a 96-well plate was added a unique aryl aldehyde (400µl of a 1M solution in THF, 14 equiv) and was followed by addition (to every well) a solution of sodium methoxide (500µl of a 0.5M solution in methanol, 8.6 equiv., *ex* Aldrich). The wells were capped and tumbled for 3-4 day.
The wells were uncapped, filtered and washed successively with the following solvents (500µl of each): THF, MeOH, THF, MeOH, THF, MeOH, THF, and pulled dry under a vacuum plenum.

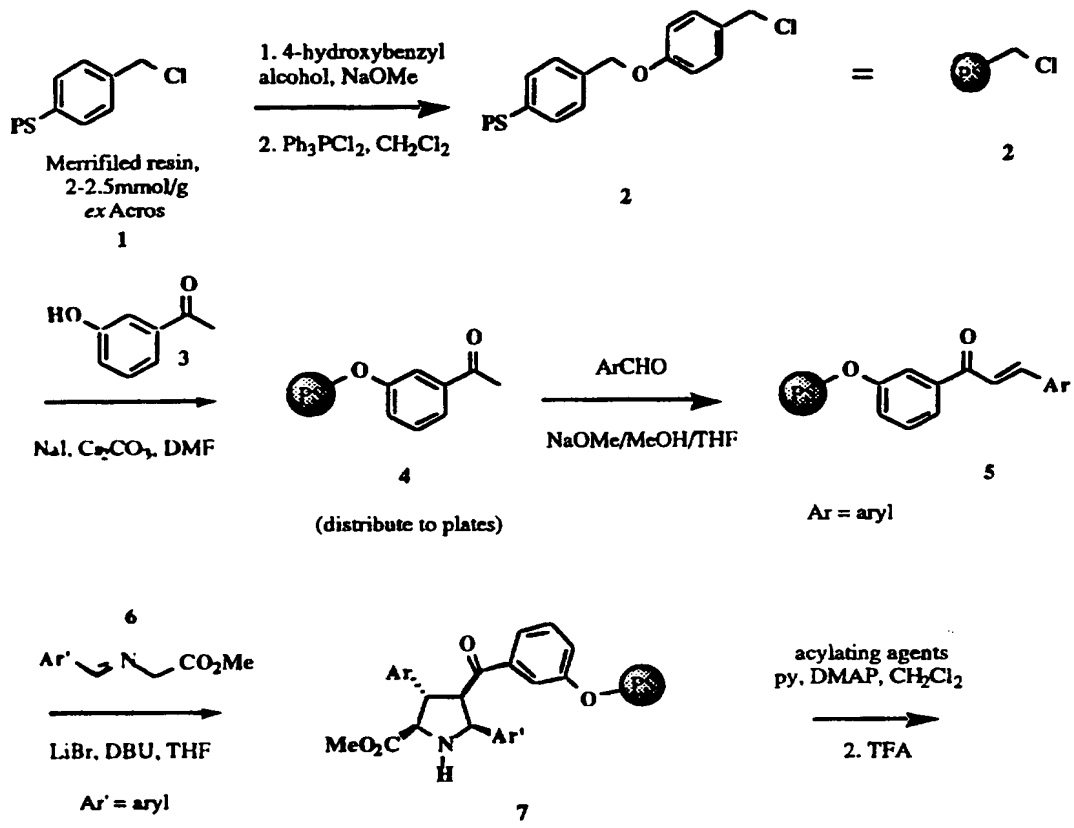
2) 1,3-Dipolar Cycloaddition Reaction: To each well was added in sequence the following reagents *via* 8-way manifold: a) benzaldehyde imine of glycine (188µl of a 1M solution in THF, 6.5equiv.), b) LiBr (500µl of a 0.5M solution in THF, 8.6equiv.) and c) DBU (188µl of a 1M solution in THF, 6.5equiv.). The wells were capped and tumbled for 3-4 days, at which time the resin was washed successively with the following solvents (500µl of each): THF, MeOH, THF, MeOH, THF, MeOH, THF, CH_2Cl_2 and pulled dry under a vacuum plenum.

3) Acylation Reaction: To each well was added *via* 8-way manifold a solution of pyridine and DMAP in CH_2Cl_2 (35.1µl pyridine and 0.53mg DMAP in 400µl CH_2Cl_2 total volume) and this was followed by a solution of unique acylating agent to each row (1-8) (400µl of 1M solution in CH_2Cl_2). The plates were capped and tumbled for 20hr, filtered and washed successively with the following solvents (500µl of each):

CH_2Cl_2, DMF, MeOH, DMF, MeOH, and CH_2Cl_2. The resin was dried under a vacuum plenum.

4) Cleavage from the Resin: To each well was added *via* 8-way manifold a solution of TFA in CH_2Cl_2 (750µl of a 10% solution). The plates were capped and tumbled for 20hr. The wells were then uncapped and allowed to gravity filter to a 1ml 96 well plate. The resin was washed with 125µl CH_2Cl_2 (each well) and the solvents evaporated in a speed-vac. TLC's were obtained after re-dissolving in 10%MeOH-CH_2Cl_2.

Experimental for Plate Synthesis



This invention is particularly well suited as a general method for preparing a structurally diverse pyrrolidine library. The final form of the library compounds in the pyrrolidine library may be as a solute dissolved in a solvent (viz., the reaction medium) or the solvent may be removed and the final product retained as a powder, paste or oil.

The reaction zone for forming each pyrrolidine library compound of this invention contains a solvent. The solvent reaction medium is typically a solvent for the reactants used.

The utility of the method of the invention and the pyrrolidine library created thereby is for developing new drugs. Pharmaceutical drug discovery relies heavily on studies of structure-activity relationships wherein the structures of discovered "lead compounds" are the basis for new drug development. The method of the invention systematically and simultaneously generates large numbers of diverse pyrrolidine molecules useful as a source of lead compounds. The combinatorial pyrrolidine libraries of the invention may be screened for pharmacologically active compounds using conventional screen protocols known in the art for any targeted disease state. Certain library compounds prepared by the process of the invention.

The successful practice of combinatorial chemistry is best done by confining reactants, products, and assay materials in specially defined arrays, adaptable to automated methods. Automated methods, optionally, software driven and computer assisted, permits full exploitation of combinatorial chemistry for diverse library preparation. For example, pipetting, diluting, dispensing, data collection, storage, plate heating/cooling, plate washing, measurements (fluorescent/radiographic/colorimetric), data

collection and high-capacity operation are all adaptable to automation.

Wellplate Apparatus containing library compounds prepared by the process of the invention:

The processes of making the pyrrolidine library of the invention may be conveniently carried out in a wellplate apparatus such as illustrated in Fig. 1 and Fig. 2, hereinafter described. It is particularly advantageous to carry out the method of the invention in a standard wellplate apparatus such as a plastic 96 well microtiter plate.

Typically, the wellplate apparatus is in the form of a rigid or semi-rigid plate, said plate having a common surface containing openings of a plurality of vessels arranged in rows and columns. A standard form of wellplate apparatus is a rectangular plastic plate having 8 rows and 12 columns (total 96) of liquid retaining depressions on its surface. A wellplate apparatus may optionally have other elements of structure such as a top or cover (e.g., plastic or foil), a bottom in a form such as a plate or reservoir, clamping means to secure the wellplate and prevent loss of its contained compounds.

The sequence of operations to be used for library generation with the wellplate is as follows:

The wellplate apparatus of the invention:

A wellplate inoculated with the novel pyrrolidine library compounds of the invention is itself a new construct or apparatus which has particular utility in an assay kit used to discover lead compounds.

A suitable system of operation and related apparatus are made as follows:

1. Reaction zones are made by drilling 96 holes in the bottom of 96 deepwell titer plates and putting a porous frit in the bottom of each well.

2. The plate is put in a clamp assembly to seal the bottom of the wells.

3. Synthesis is begun by adding reagents to their assigned plate coordinates (reaction zone).

4. The plate is capped then tumbled to mix the reagents.

5. Solid supported scavenger is added to each reaction zone after completion of the reaction is shown by thin layer chromatography.

6. After sufficient reaction time the plate is removed from the clamp and the resin washed.

7. The solution containing product is filtered and the solution collected by transfer into another 96 well plate.

8. The reaction products (library compounds) are analyzed by thin layer chromatography.

FIG. 1 illustrates the top surface of a wellplate apparatus of the invention. The wellplate (3) is a plastic plate with 96 wells (depressions) capable of holding liquids. When used in the parallel array synthesis individual reaction products are prepared in each well and are labeled by the wellplate coordinates. The shaded circles in the Figure represent wells filled with pyrrolidine library compounds prepared by the solution phase combinatorial processes of the invention. The library compound at location (1), for example, is identified by the alphanumeric coordinate, "A6."

FIG. 2 illustrates a side view of a wellplate apparatus used in the Assay Kit of the invention. The wellplate (5) contains wells (7) with a filter (9) and liquid reaction medium containing scavenger (11). The wells have an outlet at bottom which is sealed by gasket (13) held in place by

top cover (15) and bottom cover (17) maintained in position by clamp (19).

Assay Kits using wellplates with the library compounds of the invention:

This invention includes an assay kit for identification of pharmaceutical lead compounds. The assay kit comprises as essential parts, (i) wellplate apparatus (containing in its wells the pyrrolidine library compounds of the invention), and (ii) biological assay materials.

The wellplate apparatus in the kit may comprise a set of wellplate apparatus such as illustrated in Fig. 1. The library compounds contained in each wellplate may be prepared by either the pyrrolidine combinatorial library forming process taught herein. Preferably the wellplate apparatus has the form of a standard 96 well microtiter plate.

The assay kit also contains biological assay materials These biological assay materials are generally in vitro tests known to be predictive of success for an associated disease state. Illustrative of biological assay materials useful in the kit of this invention are those required to conduct the following assays:

In vitro assays:

- Enzymatic Inhibition
- Receptor-ligand binding
- Protein-protein Interaction
- Protein-DNA Interaction

Cell-based, Functional assays:

- Transcriptional Regulation
- Signal Transduction/ Second Messenger
- Viral Infectivity

Add, Incubate, & Read assays:

Scintillation Proximity Assays

- Angiotensin II SPA receptor binding assay

Endothelin converting enzyme[^{125}I] SPA assay
HIV proteinase [^{125}I] SPA enzyme assay
Cholesteryl ester transfer protein (CETP) [^{3}H] SPA assay
Fluorescence Polarization Assays
Fluorescence Correlation Spectroscopy
Colorimetric Biosensors
Ca^{2+}-EGTA Dyes for Cell-based assays
Reporter Gene Constructs for cell based assays
Luciferase, green fluorescent protein, b-lactamase
Electrical cell impedance sensor assays
Strep Potentiator Assay

The Strep Potentiator Assay is for antibiotic therapeutic indication.

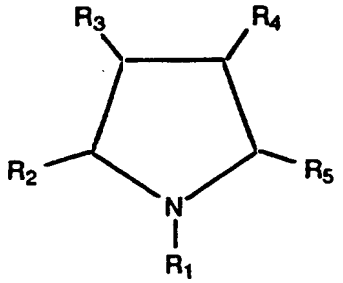
The assay has a two plate format:
Into plate 1 compounds to be tested are added with medium, methicillin, and a methicillin resistant *Staphylococcus aureus*. After an overnight incubation, the plates are read on a plate reader at 650 nm.

The utility of the pyrrolidine library compounds of this invention is illustrated by their expected positive impact in at least one of the assays cited above.

While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.

What is claimed is:

1. A library of substituted pyrrolidine compounds wherein said library contains a plurality of diverse library compounds, wherein each library compound has the formula (I):

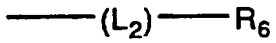


(I)

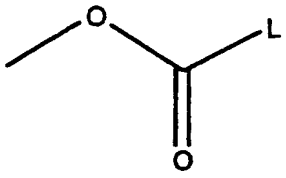
wherein;

R_1 is an electrophilic group;

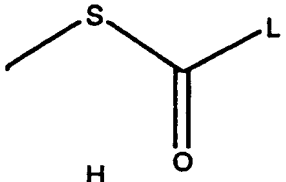
R_2 is a group represented by the formula:



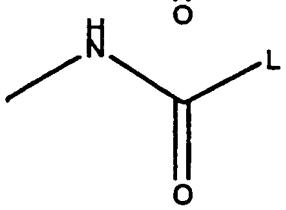
where divalent linking group $-(L_2)-$ is selected from the group consisting of,



,



and

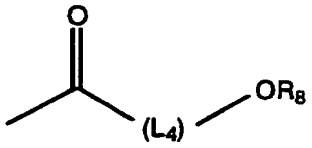


;

L is the point of attachment of the divalent group to the pyrrolidine ring, R_6 is a non-interfering substituent, and R_1 and R_2 may join together to form a hydantoin ring;

R_3 is an aromatic group;

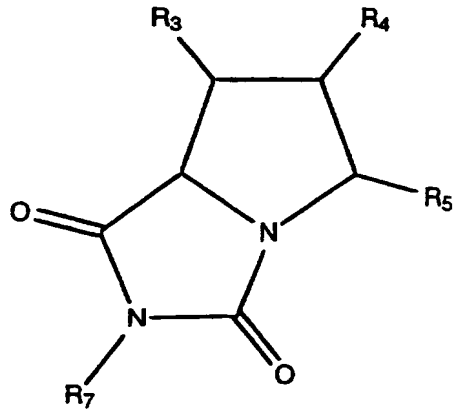
R_4 is a group of the general formula,



where -(L_4)- is a divalent linking group, R_8 is hydrogen or a non-interfering substituent; and

R_5 is an aromatic group.

2. The library of claim 1 represented by the formula (Ia),



(Ia)

wherein R_7 is a non-interfering substituent.

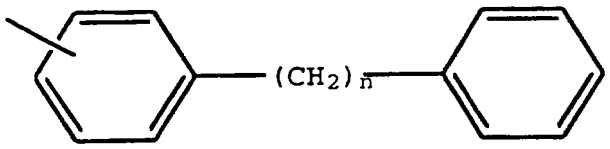
3. The pyrrolidine library of claim 1 wherein;

R_1 is an electrophilic group derived from an electrophilic reagent having a molecular weight of from about 30 to about 600 selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters,

organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates;

R_2 is $-CO_2(C_1-C_{10}$ alkyl);

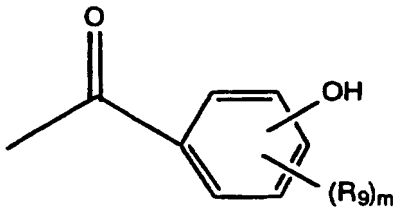
R_3 and R_5 are independently aromatic groups selected from the group consisting of substituted or unsubstituted heterocyclic groups derived from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1.2-pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pryidinyl, dipyridylyl. phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl and carbocyclic groups derived from phenyl, naphthyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (bb),



(bb)

where n is a number from 1 to 8; and

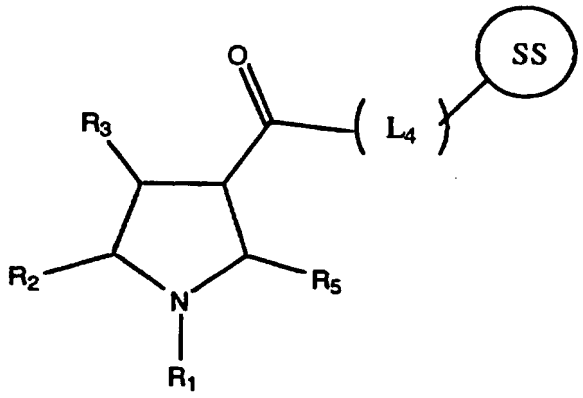
R_4 is



where R_9 is a non-interfering group and m is an integer from 0 to 3.

4. The individual substituted pyrrolidine library compounds of the library of claim 1.

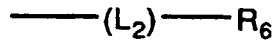
5. A library of intermediate substituted pyrrolidine compounds comprising a plurality of diverse compounds, wherein each intermediate has the formula (X):



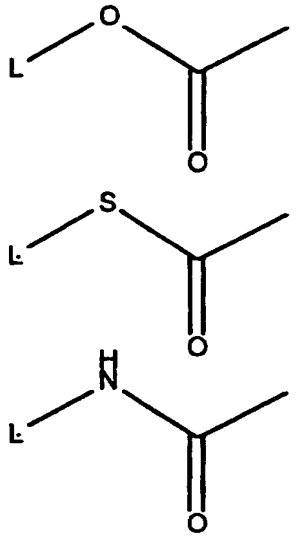
wherein;

R_1 is an electrophilic group;

R_2 is a group represented by the formula:



where divalent linking group $-(L_2)-$ is selected from the group consisting of,



and

;

L is the point of attachment of the divalent group to the pyrrolidine ring, R_6 is a non-interfering substituent, and R_1 and R_2 may join together to form a hydantoin ring;

R_3 is an aromatic group;

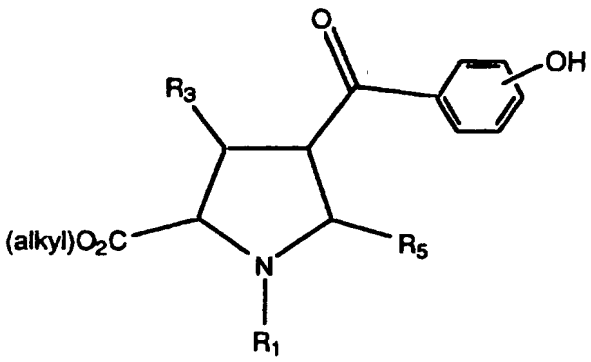
$-(L_4)-$ is a divalent linking group,

is a solid support; and

R_5 is an aromatic group.

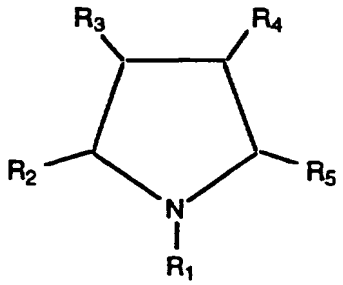
6. The intermediate substituted pyrrolidine compounds of claim 5.

7. The library of Claim 1 comprising a plurality of diverse library compounds, wherein each library compound is represented by Formula (Ia):



(Ia)

8. A combinatorial process for preparing a library of substituted pyrrolidine compounds, said library comprising a plurality of diverse library compounds, wherein each library compound is made in a separate reaction zone and is represented by the formula (I):



(I)

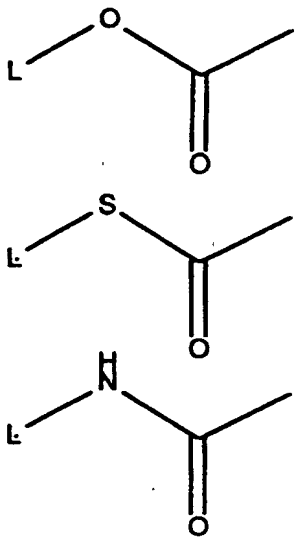
wherein;

R_1 is an electrophilic group;

R_2 is a group represented by the formula:

$$-(L_2)-R_6$$

where divalent linking group $-(L_2)-$ is selected from the group consisting of,



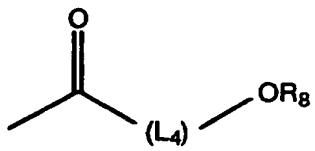
and

;

L is the point of attachment of the divalent group to the pyrrolidine ring, R_6 is a non-interfering substituent, and R_1 and R_2 may join together to form a hydantoin ring;

R_3 is an aromatic group;

R_4 is a group of the general formula,



where $-(L_4)-$ is a divalent linking group, R_8 is hydrogen or a non-interfering substituent; and

R_5 is an aromatic group;

wherein said process comprises the steps of;

A) Methyl ketone functionalizing a Wang resin solid support;

B) forming an aromatic enone on the Wang resin reaction product of Step (A);

C) reacting an azomethine ylide with the reaction product of Step (B) to effect 1,3-dipolar cycloaddition;

D) reacting an electrophile with the reaction product of Step (C) to effect electrophilic substitution on the pyrrolidine nitrogen; and

E) cleaving the substituted-diamino pyrrolidine reaction product of Step (D) from the solid support with strong acid, then recovering each pyrrolidine library compound.

9. The process of step 8 wherein;

in step (A) methyl phenyl ketone is used to functionalize the Wang resin;

in step (B) the aromatic aldehyde used to form the enone is a phenyl or substituted phenyl aldehyde;

in step (C) the azomethine ylide is a C_1-C_{10} alkyl ester of glycine; and

in step (D) the electrophilic agent has a molecular weight of from about 15 to about 600 and is selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates.

10. An assay kit for identification of pharmaceutical lead compounds, comprising biological assay materials and wellplate apparatus;

wherein the improvement comprises using as wellplate apparatus a wellplate containing in each well the individual library compounds of a diverse combinatorial pyrrolidine library prepared by the process of claim 8.

11. The assay kit of claim 10 containing biological assay materials selected from the group of assay tests;

In vitro assays:

Enzymatic Inhibition
Receptor-ligand binding
Protein-protein Interaction
Protein-DNA Interaction

Cell-based, Functional assays:

Transcriptional Regulation

Signal Transduction/ Second Messenger
Viral Infectivity
Add, Incubate, & Read assays:
Scintillation Proximity Assays
Angiotensin II SPA receptor binding assay
Endothelin converting enzyme[^{125}I] SPA assay
HIV proteinase [^{125}I] SPA enzyme assay
Cholesteryl ester transfer protein (CETP) [^{3}H] SPA assay
Fluorescence Polarization Assays
Fluorescence Correlation Spectroscopy
Colorimetric Biosensors
Ca^{2+}-EGTA Dyes for Cell-based assays
Strep Potentiator Assay.
Reporter Gene Constructs for cell based assays
Luciferase, green fluorescent protein, b-lactamase, and
Electrical cell impedance sensor assays.

12. Wellplate apparatus suitable as a replaceable element in an automated assay machine wherein the improvement comprises;

using as the wellplate apparatus a diverse pyrrolidine combinatorial wellplate, wherein each well contains a pyrrolidine library compound prepared by the method of claim 8.

13. The apparatus of claim 12 comprising a 96 well microtiter plate.

FIG.1

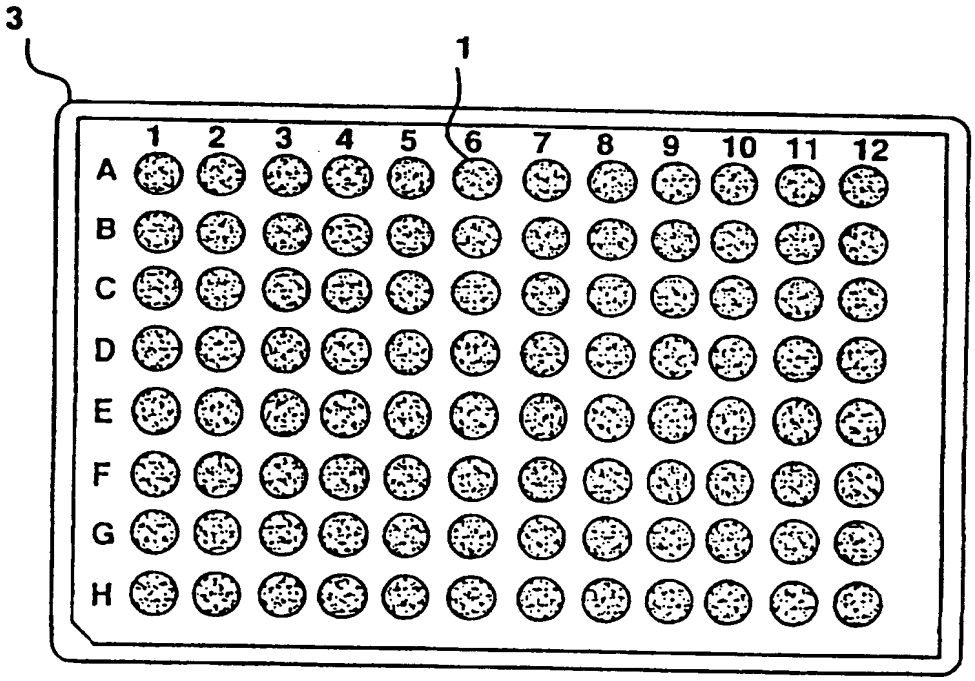
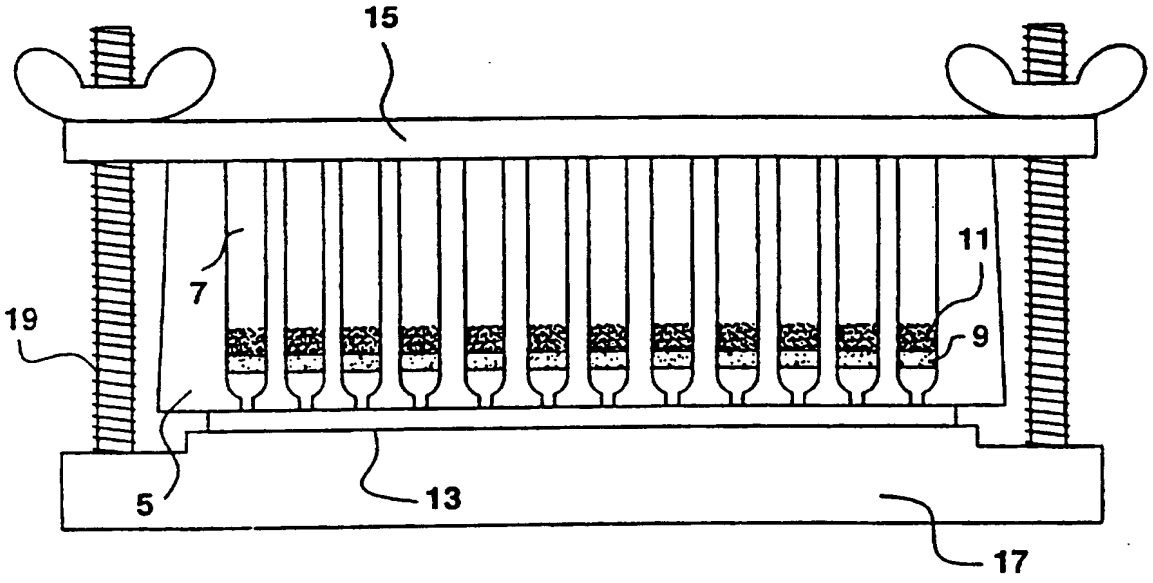


FIG.2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14559

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/237, 242, 264, 336, 353; 546/348; 548/127, 146, 215, 255, 262.2, 335.1, 440, 490, 571

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE
search terms: combinatorial, librar?, pyrrolidin?, hydantoin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,525,734 A (GALLOP et al.) 11 June 1996, see entire document.	1, 3, 7-9, 12-13
Y	US 5,525,735 A (GALLOP et al.) 11 June 1996, see entire document.	1, 3, 7-9, 12-13
Y	MURPHY et al. Combinatorial Organic Synthesis of Highly Functionalized Pyrrolidines: Identification of a Potent Angiotensin Converting Enzyme Inhibitor from a Mercaptoacyl Proline Library. J. Am. Chem. Soc. 05 July 1995, Vol. 117, No.26, pages 7029-7030, see entire document.	1, 3, 7-9, 12-13
Y	ARMSTRONG et al. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. Acc. Chem. Res. March 1996, Vol.29, No.3, pages 123-131, see entire document.	1, 3, 7-9, 12-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing f the international search report
02 OCTOBER 1997	10 NOV 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	JANE C. OSWECKI
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14559

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3, 7

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14559

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 207/08, 209/08, 209/86, 211/82, 213/34, 213/38, 213/40, 213/50, 213/56, 215/46, 233/61, 237/30, 239/20, 241/12, 241/36, 249/08, 263/32, 277/28, 285/12, 403/04, 413/04, 413/14, 417/04, 417/14, 473/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

544/237, 242, 264, 336, 353; 546/348; 548/127, 146, 215, 255, 262.2, 335.1, 440, 490, 571

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1.

Group I, claims 1, 3 and 7, drawn to a combinatorial library of pyrrolidine derivative compounds.
Group II, claim 2, drawn to a combinatorial library of hydantoin derivative compounds.
Group III, claim 4, drawn to pyrrolidine derivative compounds having quinoxaline, triazine or pyrazine as substituents.
Group IV, claim 4, drawn to pyrrolidine derivative compounds having phthalizine, pyrimidine, purine or quinazoline as substituents.
Group V, claim 4, drawn to pyrrolidine derivative compounds having thiazole, thiadiazole, oxazole, isoxazole, benzoxazole or triazole as substituents.
Group VI, claim 4, drawn to pyrrolidine derivative compounds having imidazole, indazole, carbazole or indole as substituents.
Group VII, claim 4, having imidazo-pyridine, azaindole or pyridine as substituents.
Group VIII, claims 5-6, drawn to a library of pyrrolidine derivative intermediate compounds.
Group IX, claims 10 and 11, drawn to an assay kit for pharmaceutical lead compounds.

Claims 8, 9, 12 and 13 are generic to any group paid for.

The inventions listed as Groups I-IX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I-VIII are drawn to compounds, and Group IX is drawn to an assay kit. Groups I, II and VIII are drawn to libraries of compounds with each library being drawn to compounds that differ in structure from compounds in the other two libraries and with each library of compounds not being known equivalents in the art. Groups III-VII, drawn to pyrrolidine derivative compounds, differ each from the other because no two groups share a special technical feature which makes a contribution over the prior art with any other group. Each of these groups is drawn to compounds that are structurally different and are not known as equivalents in the art.